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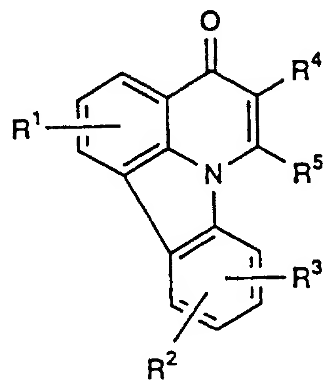
Attached documents

International Search Report

Specification and Amendment

(54) Title of invention : Pyradocarbazole derivatives with cGMP-PDE inhibitory activity



(I)

(57) English Abstract (reproduced ab-verbatim)

Novel pyridocarbazole derivatives which have a highly selective inhibitory action on cyclic GMP-PDE; a process for producing these; preventative and/or therapeutic agents for pulmonary hypertension, ischemic heart diseases, and diseases for which cGMP-PDE inhibition is effective, characterized by comprising at least one of the derivatives as the active ingredient; and intermediates useful for producing the derivatives.

(57) Japanese Language Abstract

This invention relates to novel pyridocarbazole derivatives which have a highly selective inhibitory action on cyclic GMP-phosphodiesterase (hereinafter, abbreviated to cGMP-PDE;) a process for producing these; preventative and/or therapeutic agents for pulmonary hypertension, ischemic heart diseases, and diseases for which cGMP-PDE inhibition is effective characterized by comprising at least one of the derivatives as the active ingredient and also intermediates useful for producing the pyridocarbazole derivatives.

Translator's note : In many of the sections of this patent application where production processes are outlined, the Japanese grammar used and lack of formula and reaction equation including formula, make it impossible to determine what is meant. It is almost as if the application is being deliberately obtuse. Readers of this translation should bear this in mind in particular on pages 12 to 14 and 37 to 38, and also at Claim 6.

Pyridocarbazole derivatives having cGMP-PDE inhibitory action

Technical Sphere of this invention

This invention relates to new pyridocarbazole derivatives which have a highly selective inhibiting action on cyclic GMP-phosphodiesterase (below, abbreviated to cGMP-PDE), to production processes for these, pharmaceuticals containing at least one of these as an active component and namely in particular preventives and/or therapeutic agents for pulmonary hypertension, ischaemic heart disease and diseases for which cGMP-PDE inhibition is effective, and also intermediates for use in the production of pyridocarbazole derivatives.

Technology of Prior Art

The essential body of vascular endothelium-derived relaxing factor is nitric oxide (below abbreviated to NO), and it has been elucidated that the NO generates a relaxation action on blood vessels via an increase in cyclic GMP (below, abbreviated to cGMP) in the same way as the angina drug nitroglycerine. That is to say an endogenous nitrous acid drug-like relaxing factor is present within the body, which contributes to the regulation of blood vessel constriction and the protection of an appropriate blood flow by counteracting endogenous contraction factors such as catecholamine. Accordingly, it is thought that lowering NO or cGMP will give rise to circulation disorders or ischaemic heart disease by enhancing vasoconstriction and reducing blood flow within tissues.

Vasoconstriction caused by damage to the coronary artery endothelial cells which are one type of NO synthesis cells is believed to cause insufficient blood flow in cardiac tissues and to be a causative factor of angina. This occurs due to damage to the endogenous relaxation factor NO-cGMP system. The vasodilating effect of the nitrous acid drug shows site specificity of action with differing extents of relaxation being afforded according to the blood vessel diameter, wherein as the larger coronary arteries are relaxed more strongly, the said drug has been subject to frequent use so far. However, there is the problem that the duration of the action of the nitrous acid drug is brief and the action weakens with long term use. Moreover, among the vasodilating drugs, as far as the adenosine enhancing drugs such as dipyridamole, which increase the coronary artery blood flow by dilating the fine parts of the coronary artery are concerned, these have shown indications of demonstrating side effects of aggravating angina and chest pain, because they worsen ischemia by causing increases in the myocardial blood flow at healthy sites rather than diseased lesions (this is known as the 'steal phenomenon').

Most recently, the effective use of NO gas inhalation treatment has been reported for various disease conditions which present pulmonary hypertension for which there have not been effective drugs to date. Because NO gas causes relaxation of the blood vessels through an increase in cGMP and a consequential lowering of the pulmonary blood pressure, it may be expected that the activation of the cGMP production system in the pulmonary circulation will dilate the pulmonary arteries selectively, and will lead to a treatment of pulmonary hypertension. Until now, starting with calcium blockers, many vasodilator drugs have been studied for treating pulmonary hypertension, but all of them have a greater effect for lowering the systemic blood pressure than the pulmonary blood pressure and none has reached a practical application stage. The therapy with which an effect for improvement of the prognosis has been confirmed with is oxygen therapy. However, oxygen toxicity occurs as a serious side effect, and in patients for whom long term domestic oxygen treatment has been prescribed, the generation of pathological changes in the lungs such as pulmonary oedema, pulmonary fibrosis and the like has been reported. Moreover, even in NO gas inhalation treatment, because the NO gas used is one of the NOx atmospheric pollutants, and NO_2 is readily generated in the copresence of oxygen, there is also a possibility of a harmful effect being demonstrated on the bronchus and lung, the administration necessitates great care and there are many difficulties in its long-term use. It is also believed that it should be possible to maintain the cGMP concentration and to reduce pulmonary arterial pressure selectively by depressing the cGMP decomposition system. In other words, inhibitors of the enzyme phosphodiesterase (below, abbreviated to PDE) which catalyse the decomposition of cyclic GMP selectively may be expected to form a new therapeutic agent which will not have such side effects.

Thus, if PDE is inhibited in this way, cGMP will increase, which would be thought to lead to a treatment of these conditions, but the presence of at least seven isozymes in PDE has been confirmed so far. Among these, five isozymes are commonly distributed widely in many tissues. There are two isozymes which decompose cGMP selectively; namely PDE type I (calmodulin-dependent PDE) and PDE type V (cGMP-PDE). While on the other hand, PDE type III and PDE type IV decompose cAMP selectively, and PDE type II is not substrate selective. If the latter three isozymes are inhibited, cAMP will increase and the generation of various side effects may be readily anticipated, such as increased myocardial contraction power, raised pulse rate, lowered systemic blood pressure and the like. In particular, increased cAMP and increased myocardial contraction due to PDE III inhibition is well known. Moreover, there are also reports that the contraction force decreases when cGMP increases in the myocardium, but the distribution of PDE V in the myocardium

has not been confirmed. Accordingly, as a result of selective inhibition of PDE V, a selective action may be expected wherein there is an action of lowering the systemic blood pressure and a small side effect on the heart.

Moreover recently, compounds that release NO have been found to show suppression of vascular smooth muscle cell proliferation via cGMP. For example, Garg et al. (J. Clin. Invest., Vol 83, pp. 1774-1777, 1989), Nakaki et al. (Eur. J. Pharmacol., Vol 189, pp. 347-353, 1990) reported that when 8-bromo-cGMP or compounds such as nitroprusside, nitroglycerine and isosorbide nitrate which release NO were caused to act on cultured vascular smooth muscle cells obtained from rat aorta tunica media, the proliferation thereof was suppressed. Accordingly, it is suggested that an increase in cGMP will lead to a suppression of vascular smooth muscle cell proliferation in arteriosclerosis and post-PTCA restenosis.

So far, as cGMP-PDE inhibitors, for example, pyrazolopyrimidone derivatives have been disclosed in EP 526004, purinone derivatives in Kokai 2-88577, phenylpyrimidone derivatives in Kokai H2-295978, quinazoline derivatives in Kokai 6-192235, JP07-10843 and WO 93/12095, and phthalazine derivatives in WO 96/05176. However, cGMP-PDE inhibiting action in compounds having a pyridocarbazole structure such as the compounds of this invention have not been disclosed in the technology of prior art. Moreover, as far as the PDE isozyme selectivity is concerned, isozyme selectivity between type III and type V is disclosed in EP 526004 and WO 93/12095, but up to now, a practical form which gives sufficient action in the clinical field based on this selectivity has not been attained.

Moreover, when pyridocarbazole derivatives have been investigated, PDE inhibition activity has not been reported until now, and there has been no report of a vasodilating action, and moreover, there have been no reports of efficacy in pulmonary hypertension and ischaemic heart disease.

The object of this invention is to put forward new compounds having a strong cGMP-PDE inhibiting action with high enzyme selectivity, and which moreover have less side effects and high safety.

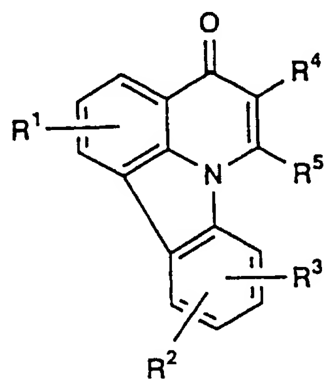
Moreover, a further object of this invention is to put forward production processes for these, intermediates useful for the production of these, and pharmaceuticals and pharmaceutical compositions containing these. In particular, an object of this invention is to put forward preventive

and therapeutic agents for pulmonary hypertension, ischaemic heart disease, and diseases wherein cGMP-PDE inhibition is effective, and which overcome at least one of the aforesaid problems of the prior art.

Detailed Description of this Invention

The inventors carried out assiduous investigations in order to obtain a drug which strongly and selectively inhibited PDE V and had high safety, and as a result discovered new pyridocarbazole derivatives and salts thereof which have a potent and selective PDE V inhibition activity. This invention was completed on the basis of this discovery.

The first form of this invention is a compound represented by following formula (I),



(I)

(in the formula, R^1 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, alkoxycarbonyl group of carbon number 1-4, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, 2-hydroxypentyloxy group, 2,2-diethoxyethoxy group, optionally protected hydroxy group, optionally protected mercapto group, straight chain or branched chain alkanoyloxy group of carbon number 1-4, carbonyloxy group substituted by a phenyl group or pyridyl group, straight chain or branched chain alkyl group of carbon number 1-4 optionally substituted by one hydroxy group, an amino group optionally mono- or di-substituted by an alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3 optionally mono-substituted by a group arbitrarily selected from a hydroxy group • carboxyl group • phenyl group or pyridyl group, or following formula (XXI)

$$-O-(CH_2)_n-Z \quad (XXI)$$

(in the formula, Z denotes a hydrogen atom, carboxyl group, alkoxy group of carbon number 1 or 2 optionally substituted by one hydroxy group, alkoxycarbonyl group of carbon number 1-6, carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or alkyl group of carbon number

1 or 2, alkanoyl group of carbon number 1-4 optionally substituted by one hydroxy group or mercapto group, piperidinylcarbonyl group optionally substituted by one carboxyl group or alkoxy carbonyl group of carbon number 1 or 2, morpholylcarbonyl group, hydroxy group, mercapto group, amino group, phenyl group, pyridyl group optionally mono-substituted by a hydroxymethyl group • acetoxymethyl group • alkyl group of carbon number 1-4 or alkoxycarbonyl group of carbon number 1 or 2, pyrazinyl group, pyrimidinyl group, furyl group, thienyl group, oxadiazolyl group, 4-methoxyphenoxy group, and n denotes 1 to 6);

R^2 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, 4-morpholylacetyl group, straight chain or branched chain alkanoyloxy group of carbon number 1-4, straight chain or branched chain alkanoyl group of carbon number 1-4, straight chain or branched chain alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3 optionally mono-substituted by a group arbitrarily selected from a hydroxy group • carboxyl group • phenyl group or pyridyl group, or straight chain or branched chain alkoxy group of carbon number 1-4 optionally substituted by one alkoxycarbonyl group of carbon number 1-4;

R^3 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group or straight chain or branched chain alkoxy group of carbon number 1-4;

R^4 denotes a hydrogen atom, halogen atom, optionally protected carboxyl group, phenoxy group, anilino group, N-methylanilino group, 4-morpholylcarbonyl group, alkyl group of carbon number 1 or 2 optionally substituted by a cyclic alkyl group of carbon number 3-6, benzyl group optionally mono- or di-substituted on the phenyl moiety with a group arbitrarily selected from a halogen atom • hydroxy group • mercapto group • alkoxy group of carbon number 1 or 2 • alkylthio group of carbon number 1 or 2 • alkoxycarbonyl group of carbon number 1-4 • acetylamino group • carboxyl group or amino group, pyridylmethyl group optionally substituted by an alkyl group of carbon number 1-4, morpholyl methyl group, triazolylmethyl group, furylmethyl group, thienylmethyl group, pyrimidinylmethyl group, pyrazinylmethyl group, pyrrolylmethyl group, imidazolylmethyl group, quinolylmethyl group, indolylmethyl group, naphthylmethyl group, benzoyl group, α-hydroxybenzyl group, or an alkoxycarbonyl group of carbon number 1 or 2;

R^5 denotes a hydrogen atom or methyl group;

when R^1, R^2, R^3 and R^5 are simultaneously hydrogen atoms, R^4 is not a hydrogen atom, benzyl group, 4-diethylaminobenzyl group or furylmethyl group)

or a salt thereof, or a drug containing such a compound or a salt as an effective component.

In the aforesaid compound represented by the formula (I), preferred substituents and preferred combinations thereof are described below but this invention is not limited to these.

The preferred substitution position for R^1 is the 2-position, and R^1 is preferably a hydroxy group, or of following formula (XXI)

$-O-(CH_2)_n-Z$ (XXI)

(in the formula, Z denotes a hydrogen atom, carboxyl group, alkoxycarbonyl group of carbon number 1-6, carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or alkyl group of carbon number 1 or 2, alkanoyl group of carbon number 1-4 optionally substituted by one hydroxy group or mercapto group, hydroxy group, amino group, phenyl group, pyridyl group optionally mono-substituted by a hydroxymethyl group • acetoxymethyl group • alkyl group of carbon number 1-4 or alkoxycarbonyl group of carbon number 1 or 2, pyrazinyl group, or pyrimidinyl group, and n denotes 1 to 4);

More preferably, R^1 is in the 2-position, and R^1 is a hydroxy group, or of following formula (XXI)

$-O-(CH_2)_n-Z$ (XXI)

(in the formula, Z denotes a hydrogen atom, carboxyl group, carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or alkyl group of carbon number 1 or 2, alkanoyl group of carbon number 1-4 optionally substituted by one hydroxy group or mercapto group, hydroxy group, phenyl group, pyridyl group, pyrazinyl group, pyrimidinyl group, and n denotes 1 to 4);

Preferably, R^2 and R^3 are not simultaneously hydrogen atoms, the substitution position of R^2 is position 9 or 10, and R^2 is a hydrogen atom, halogen atom, hydroxy group, trifluoromethyl group or straight chain or branched chain alkoxy group of carbon number 1-4, and R^3 is a hydrogen atom. Further, preferably the position of substitution of R^2 is the 9-position and R^2 is a halogen atom or trifluoromethyl group, R^3 is a hydrogen atom, and R^4 is a hydrogen atom, alkyl group of carbon number 1 or 2, pyrimidinylmethyl group, or pyridylmethyl group optionally substituted by a methyl group. More preferably, R^4 is a methyl group pyrimidinylmethyl group or pyridylmethyl group. Preferably R^5 is a hydrogen atom.

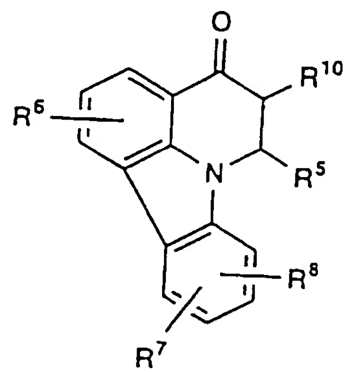
As a combination of substituents, preferably R^1 is in the 2-position, and R^1 is a hydroxy group, or of following formula (XXI)

$-O-(CH_2)_n-Z$ (XXI)

(in the formula, Z denotes a hydrogen atom, carboxyl group, carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or alkyl group of carbon number 1 or 2, alkanoyl group of carbon number 1-4 optionally substituted by one hydroxy group or mercapto group, hydroxy group,

phenyl group, pyridyl group, pyrazinyl group, or pyrimidinyl group, and n denotes 1 to 4); R^2 is a halogen atom or trifluoromethyl group in position 9, R^3 is a hydrogen atom, R^4 is a methyl group, pyrimidinylmethyl group or pyridylmethyl group, and R^5 is a hydrogen atom.

Moreover, a second form of this invention is a compound or a salt thereof represented by following formula (IV), which is an intermediate used for the synthesis of the aforesaid compound of formula (I) or a salt thereof.

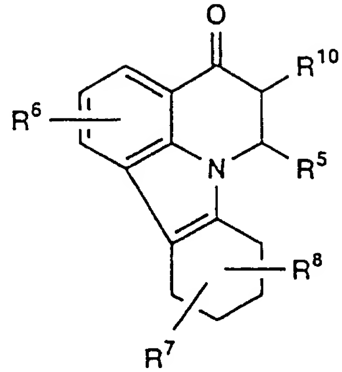


(IV)

(in the formula, R^5 is a hydrogen atom or methyl group, R^6 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, alkoxycarbonyl group of carbon number 1-4, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, optionally protected hydroxy group, optionally protected mercapto group, straight chain or branched chain alkyl group of carbon number 1-4 optionally substituted by one hydroxy group, an amino group optionally mono- or di-substituted by an alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3, or straight chain alkoxy group of carbon number 1-6 optionally substituted by a 4-methoxyphenoxy group; R^7 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, straight chain or branched chain alkanoyl group of carbon number 1-4, straight chain or branched chain alkyl group of carbon number 1-4, straight chain or branched chain alkoxy group of carbon number 1-4; R^8 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, or straight chain or branched chain alkoxy group of carbon number 1-4; R^{10} denotes a hydrogen atom, halogen atom, phenoxy group, α-hydroxybenzyl group, anilino group, N-methylanilino group, methyl group, or halomethyl group).

Moreover, a third form of this invention is the use of a compound represented by the following formula (VIII) or a salt thereof as an intermediate useful for the synthesis of a compound of the

aforesaid formula (I) or a salt thereof.



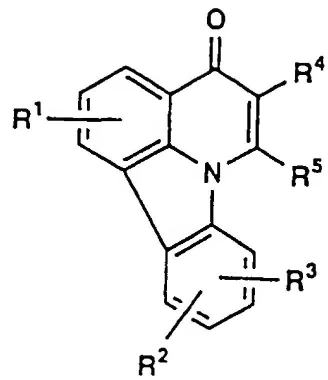
(VIII)

(in the formula, R^5 is a hydrogen atom or methyl group, R^6 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, alkoxycarbonyl group of carbon number 1-4, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, optionally protected hydroxy group, optionally protected mercapto group, straight chain or branched chain alkyl group of carbon number 1-4 optionally substituted by one hydroxy group, an amino group optionally mono- or di-substituted by an alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3, or straight chain alkoxy group of carbon number 1-6 optionally substituted by a 4-methoxyphenoxy group; R^7 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, straight chain or branched chain alkanoyl group of carbon number 1-4, straight chain or branched chain alkyl group of carbon number 1-4, or straight chain or branched chain alkoxy group of carbon number 1-4; R^8 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, or straight chain or branched chain alkoxy group of carbon number 1-4; R^{10} denotes a hydrogen atom, halogen atom, phenoxy group, α-hydroxybenzyl group, anilino group, N-methylanilino group, methyl group, or halomethyl group).

Moreover, a fourth form of this invention comprises production processes for the aforesaid derivative compound of the aforesaid formula (I) (Production Processes 1-3).

[Production Process 1]

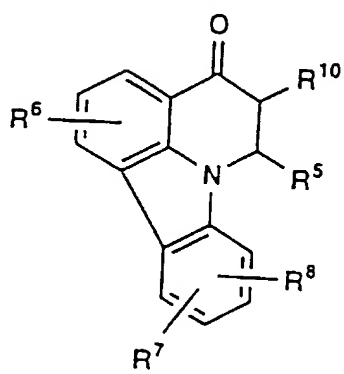
A process for production of a compound represented by following formula (I)



(I)

(in the formula, R^1, R^2, R^3 and R^4 have the same aforesaid meanings, and R^5 denotes a hydrogen atom or a methyl group) or a salt thereof,

wherein a compound represented by the following formula (IV) or a salt thereof



(IV)

(in the formula, R^5 has the same aforesaid meaning, R^6 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, alkoxycarbonyl group of carbon number 1-4, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, optionally protected hydroxy group, optionally protected mercapto group, straight chain or branched chain alkyl group of carbon number 1-4 optionally substituted by one hydroxy group, an amino group optionally mono- or di-substituted by an alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3, or straight chain alkoxy group of carbon number 1-6 optionally substituted by a 4-methoxyphenoxy group; R^7 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, straight chain or branched chain alkanoyl group of carbon number 1-4, straight chain or branched chain alkyl group of carbon number 1-4, or straight chain or branched chain alkoxy group of carbon number 1-4; R^8 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, or straight chain or branched chain alkoxy group of carbon number 1-4; and R^{10} denotes a hydrogen atom, halogen atom, phenoxy group, α-hydroxybenzyl group, anilino

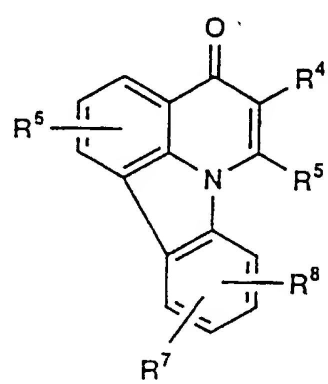
group, N-methylanilino group, methyl group, or halomethyl group)

is reacted, if necessary under basic conditions, with an aldehyde derivative of following formula (XIX)

R^{12}-CHO (XIX)

(in the formula, R^{12} denotes a hydrogen atom, methyl group, cyclic alkyl group of carbon number 3-6, phenyl group optionally mono- or di-substituted by a group arbitrarily selected from a halogen atom, • hydroxy group • mercapto group • alkoxy group of carbon number 1 or 2 • alkylthio group of carbon number 1 or 2 • alkoxycarbonyl group of carbon number 1-4 • acetylamino group • carboxyl group or amino group, pyridyl group optionally substituted by an alkyl group of carbon number 1-4, morpholyl group, triazolyl group, furyl group, thienyl group, pyrimidinyl group, pyrazinyl group, pyrrolyl group, imidazolyl group, quinolyl group, indolyl group, or naphthyl group),

and thereafter the compound as it is or the compound wherein the double bond in the ring of the enone formed by dehydration is isomerized in the ring, is subjected to an oxidation reaction, or is reacted with phenol, aniline, N-methyl aniline, triazole, imidazole, morpholine or the like, and thereafter an oxidation reaction carried out, or a compound represented by following formula (XXII) is derived by an oxidation reaction



(XXII)

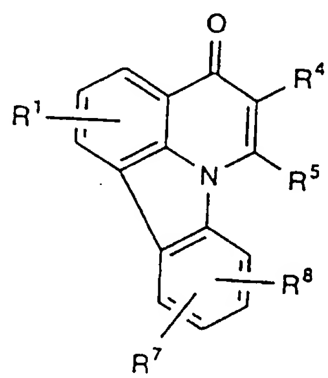
(in the formula, R^4, R^5, R^6, R^7 and R^8 have the same aforesaid meanings), or a suitable substituent conversion is carried out or in accordance with requirements deprotection of R^6 is carried out,

and then a reaction is caused with a reactive halogen derivative represented by following formula (XX)

R^{13}-X (XX)

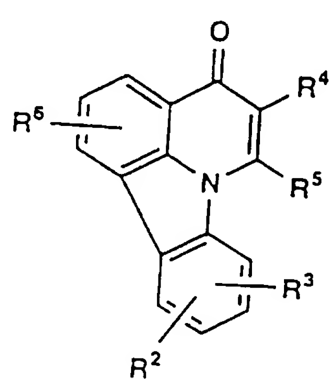
(in the formula, X denotes a halogen atom, R^{13} denotes an alkoxycarbonyl group of carbon number 1-4, 3-carboxy-1-propenyl group, 2,2-diethoxyethyl group, straight chain or branched alkanoyl group of carbon number 1-4, carbonyl group substituted by a phenyl group or pyridyl group, or group: -$(CH_2)_n$-Z (Z denotes a hydrogen atom, carboxyl group, alkoxy group optionally substituted by one hydroxy group, alkoxycarbonyl group of carbon number 1-6, carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or alkyl group of carbon number 1-2, alkanoyl group of

carbon number 1-4 optionally substituted by one hydroxy group or mercapto group, piperidinylcarbonyl group optionally substituted by one carboxyl group or alkoxycarbonyl group of carbon number 1-2, morpholylcarbonyl group, hydroxy group, mercapto group, amino group, phenyl group, pyridyl group optionally mono-substituted by a hydroxymethyl group • acetoxymethyl group • alkyl group of carbon number 1-4 or alkoxycarbonyl group of carbon number 1-2, pyrazinyl group, pyrimidinyl group, furyl group, thienyl group, oxadiazolyl group, 4-methoxyphenoxy group, and n denotes 1 to 6)), and a compound represented by following formula (XXIII) is obtained



(XXIII)

(in the formula, R^1, R^4, R^5, R^7 and R^8 have the same aforesaid meanings),
and a suitable substituent conversion is carried out, or a suitable substituent conversion is carried out from the compound of the aforesaid formula (XXII), and a compound represented by following formula (XXIV)

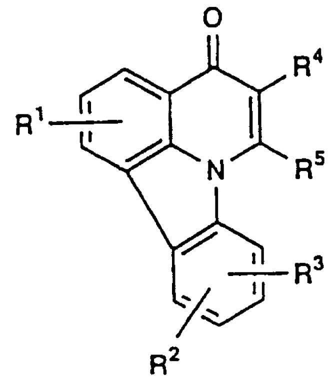


(XXIV)

(in the formula, R^2, R^3, R^4, R^5 and R^6 have the same aforesaid meanings) is obtained, and thereafter in accordance with requirements, deprotection of R^6 is carried out, and a reaction is caused with a reactive halogen derivative represented by aforesaid formula (XX), and thereby is produced.

[Production Process 2]

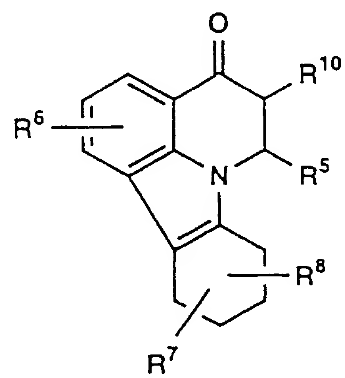
A process for the production of a compound represented by following formula (I) or a salt thereof



(I)

(wherein, R^1, R^2, R^3, R^4 and R^5 have the same aforesaid meanings) comprising carrying out procedures, such that

a compound represented by following formula (VIII)



(VIII)

(wherein, R^5, R^6, R^7, R^8 and R^{10} have the same aforesaid meanings) or a salt thereof is reacted with an aldehyde derivative represented by following formula (XIX)

$$R^{12}\text{-CHO} \qquad (XIX)$$

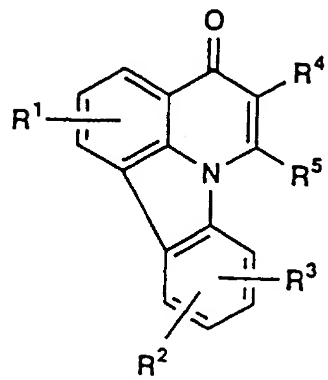
(wherein, R^{12} has the same aforesaid meaning) under basic conditions in accordance with requirements, and thereafter, without further treatment or as the compound formed wherein the double bond of the enone formed by dehydration is isomerized in the ring; or after reaction with phenol, aniline, N-methylaniline, triazole, imidazole, morpholine or the like, is subject to an oxidation reaction, and thereafter, the compound obtained by the aromatic ring formation reaction using an oxidising agent is deprotected in accordance with requirements and reacted with a reactive halogen derivative represented by following formula (XX)

$$R^{13}\text{-X} \qquad (XX)$$

(wherein, X and R^{13} have the same aforesaid meanings), or a suitable substituent conversion is carried out.

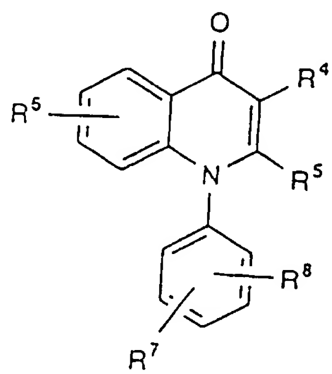
[Production Process 3]

A process for the production of a compound represented by following formula (I) or a salt thereof



(I)

(wherein, R^1, R^2, R^3, R^4 and R^5 have the same aforesaid meanings) by subjecting a compound represented by following formula (XIII)



(XIII)

(wherein, R^4 denotes a hydrogen atom, halogen atom, optionally protected carboxyl group, phenoxy group, anilino group, N-methylanilino group, 4-morpholyl carbonyl group, 1-2C alkyl group optionally substituted by a 3-6C cyclic alkyl group, benzyl group optionally mono- or di-substituted on the phenyl moiety by 1 or 2 groups arbitrarily selected from a halogen atom, hydroxy group, mercapto group, 1-2C alkoxy group, 1-2C alkylthio group, 1-4C alkoxycarbonyl group, acetylamino group, carboxyl group or amino group, pyridylmethyl group optionally substituted by a 1-4C alkyl group, morpholyl methyl group, triazolyl methyl group, furyl methyl group, thienylmethyl group, pyrimidinyl methyl group, pyrazinyl methyl group, pyrrolylmethyl group, imidazolylmethyl group, quinolyl methyl group, indolyl methyl group, naphthyl methyl group, benzoyl group, α-hydroxy benzyl group or 1-2C alkoxycarbonyl group; R^5 denotes a hydrogen atom or methyl group; R^6 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, 1-4C alkoxycarbonyl group, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, optionally protected hydroxy group, optionally protected mercapto group, 1-4C straight or branched chain alkyl group optionally substituted by one

hydroxy group, amino group optionally mono- or di-substituted by a 1-4C alkyl group, 1-3C alkylthio group or 1-6C straight chain alkoxy group optionally substituted by a 4-methoxyphenoxy group; R^7 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, 1-4C straight or branched chain alkanoyl group, 1-4C straight or branched chain alkyl group or 1-4C straight or branched chain alkoxy group; and R^8 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group or 1-4C straight or branched chain alkoxy group) or a salt thereof to an aromatic carbon-carbon bond forming reaction using palladium and in accordance with requirements carrying out suitable substituent conversion.

Moreover, a fifth form of this invention is a preventive agent or therapeutic agent for pulmonary hypertension, containing as effective component, at least one compound represented by aforesaid formula (I) or a salt thereof.

Moreover, a sixth form of this invention is a preventive agent or therapeutic agent for ischemic heart disease containing as effective component, at least one compound represented by the aforesaid formula (I) or a salt thereof.

Moreover, a seventh form of this invention is a preventive agent or therapeutic agent for a disease wherein cGMP-PDE inhibitory action is effective, containing as effective component, at least one compound represented by the aforesaid formula (I) or a salt thereof.

Brief Description of the Figures

Figure 1 is a figure illustrating Example 278 and showing structural formulae of intermediates in the Examples.

Figure 2 is a figure showing structural formulae of intermediates in the Examples.

Figure 3 is a figure showing structural formulae of intermediates in the Examples.

Figure 4 is a figure showing structural formulae of intermediates in the Examples.

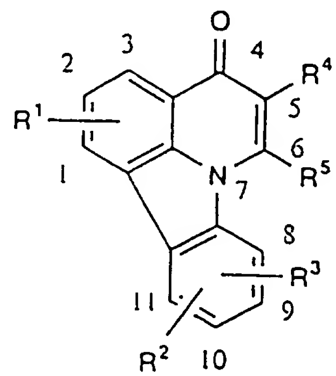
Figure 5 is a figure showing structural formulae of intermediates in the Examples.

Figure 6 is a figure showing structural formulae of intermediates in the Examples.

Ideal Form for Carrying Out this invention

Hereinafter, this invention will be described in greater detail.

The position numbering of the pyridocarbazole derivatives comprising the compounds of this invention is as indicated in the figure below, and the bonding position of R^1 is the 1-, 2- or 3-position, the bonding position of R^2 or R^3 is the 8-, 9-, 10- or 11-position, the bonding position of R^4 is the 5-position and the bonding position of R^5 is the 6-position.



(I)

The compound of this invention is represented by aforesaid formula (I).

In the formula, R^1 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, 1-4C alkoxycarbonyl group, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, 2-hydroxy pentyloxy group, 2,2-diethoxy ethoxy group, optionally protected hydroxy group, optionally protected mercapto group, 1-4C straight or branched chain alkanoyloxy group, carbonyloxy group substituted by a phenyl group or pyridyl group, 1-4C straight or branched alkyl group optionally substituted by one hydroxy group, amino group optionally mono- or di-substituted by a 1-4C alkyl group, 1-3C alkylthio group optionally mono-substituted by a member arbitrarily selected from the group comprising a hydroxy group, carboxyl group, phenyl group and pyridyl group or the following formula (XXI)

$$-O-(CH_2)_n-Z \quad (XXI)$$

(wherein, Z denotes a hydrogen atom, carboxyl group, alkoxy group of carbon number 1 or 2 optionally substituted by one hydroxy group, 1-6C alkoxycarbonyl group, carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or 1-2C alkyl group, alkanoyl group of carbon number 1 to 4 optionally substituted by one hydroxy group or mercapto group, piperidinyl carbonyl group optionally substituted by one carboxyl group or 1-2C alkoxycarbonyl group, morpholyl carbonyl group, hydroxy group, mercapto group, amino group, phenyl group, pyridyl group optionally mono-substituted by a hydroxymethyl group, acetoxymethyl group, 1-4C alkyl

group or 1-2C alkoxycarbonyl group, pyrazinyl group, pyrimidinyl group, furyl group, thienyl group, oxadiazolyl group or 4-methoxyphenoxy group, and n denotes 1-6).

More precisely, halogen atom denotes a fluorine atom, chlorine atom or bromine atom; 1-4C alkoxycarbonyl group denotes a methoxycarbonyl group, ethoxycarbonyl group, n-propoxy carbonyl group, i-propoxy carbonyl group, cyclopropoxy carbonyl group, n-butoxycarbonyl group, t-butoxy carbonyl group and the like; optionally protected hydroxy group denotes a hydroxy group, trimethylsilyloxy group, t-butyldimethylsilyloxy group, methoxymethyloxy group and the like; optionally protected mercapto group denotes a phenylthio group, benzylthio group and the like; 1-4C straight chain or branched alkanoyloxy group denotes an acetoxy group, propionyloxy group, butyryloxy group, pivaloyloxy group and the like; carbonyloxy group substituted by a phenyl group or pyridyl group denotes a benzoyloxy group, nicotinoyloxy group, isonicotinoyloxy group and the like; 1-4C straight or branched chain alkyl group optionally substituted by one hydroxy group denotes a methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, t-butyl group, 1-hydroxyethyl group, 2-hydroxyethyl group, 1-hydroxypropyl group and the like; amino group optionally mono- or di-substituted by a 1-4C alkyl group denotes a methylamino group, dimethylamino group, ethylamino group, diethylamino group, n-propylamino group, n-butyl amino group and the like; 1-3C alkylthio group optionally mono-substituted by a group arbitrarily selected from the group comprising a hydroxy group, carboxyl group, phenyl group and pyridyl group denotes a methylthio group, ethylthio group, 3-hydroxypropyl thio group, carboxymethyl thio group, 3-pyridylmethyl thio group; and the following formula (XXI)

$$-O-(CH_2)_n-Z \quad (XXI)$$

(wherein, Z denotes a hydrogen atom, carboxyl group, alkoxy group of carbon number 1 or 2 optionally substituted by one hydroxy group, 1-6C alkoxycarbonyl group, carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or 1-2C alkyl group, alkanoyl group of carbon number 1 to 4 optionally substituted by one hydroxy group or mercapto group, piperidinyl carbonyl group optionally substituted by one carboxyl group or 1-2C alkoxycarbonyl group, morpholyl carbonyl group, hydroxy group, mercapto group, amino group, phenyl group, pyridyl group optionally mono-substituted by a hydroxymethyl group, acetoxymethyl group, 1-4C alkyl group or 1-2C alkoxycarbonyl group, pyrazinyl group, pyrimidinyl group, furyl group, thienyl group, oxadiazolyl group or 4-methoxyphenoxy group, and n denotes 1-6) denotes a methoxy group, ethoxy group, n-propoxy group, n-butoxy group, n-pentyloxy group, n-hexyloxy group, carboxymethyloxy group, 2-carboxyethyloxy group, 3-carboxypropyloxy group, methoxymethoxy

group, ethoxy methoxy group, 2-methoxyethoxy group, 2-ethoxy ethoxy group, 2-(2-hydroxyethoxy) ethoxy group, methoxycarbonylmethyloxy group, ethoxy carbonyl methyloxy group, n-propoxy carbonyl methyloxy group, i-propoxy carbonyl methyloxy group, n-butoxycarbonyl methyloxy group, t-butoxycarbonyl methyloxy group, n-pentyloxy carbonyl methyloxy group, n-hexyloxy carbonyl methyloxy group, cyclopropyloxycarbonyl methyloxy group, cyclohexyloxycarbonyl methyloxy group, 2-(methoxycarbonyl) ethyloxy group, 2-(ethoxycarbonyl) ethyloxy group, 2-(n-propoxy carbonyl) ethyloxy group, 2-(i-propoxy carbonyl) ethyl oxo group, 2-(n-butoxycarbonyl) ethyloxy group, 2-(t-butoxycarbonyl) ethyloxy group, 2-(n-pentyloxy carbonyl) ethyloxy group, 2-(n-hexyloxy carbonyl) ethyloxy group, 2-(cyclopropyloxycarbonyl) ethyloxy group, 2-(cyclohexyloxy carbonyl) ethyloxy group, 3-(methoxycarbonyl) propyloxy group, 3-(ethoxycarbonyl) propyloxy group, 3-(n-propoxy carbonyl) propyloxy group, 3-(i-propoxy carbonyl) propyloxy group, 3-(n-butoxycarbonyl) propyloxy group, 3-(t-butoxycarbonyl) propyloxy group, 3-(n-pentyloxy carbonyl) propyloxy group, 3-(n-hexyloxy carbonyl) propyloxy group, 3-(cyclopropyloxycarbonyl) propyloxy group, 3-(cyclohexyloxycarbonyl) propyloxy group, N-hydroxymethyl carbamoylmethyloxy group, N-methylcarbamoyl methyloxy group, N,N-dimethylcarbamoylmethyloxy group, N-ethyl carbamoylmethyl oxy group, N,N-diethylcarbamoyl methyloxy group, N-n-propyl carbamoylmethyloxy group, N-n-butyl carbamoylmethyloxy group, 3-hydroxy-2-oxopropyloxy group, 4-hydroxy-3-oxobutyloxy group, 5-hydroxy-4-oxo pentyloxy group, 4-hydroxy-2-oxobutyloxy group, 5-hydroxy-2-oxo pentyloxy group, 6-hydroxy-2-oxohexyloxy group, 5-mercapto-2-oxo pentyloxy group, 4-carboxy-1-piperidinyl carbonyl methyloxy group, 4-methoxy carbonyl-1-piperidinyl carbonyl methyloxy group, 4-ethoxycarbonyl-1-piperidinyl carbonyl methyloxy group, 4-morpholyl carbonyl methyloxy group, 2-hydroxyethyloxy group, 3-hydroxypropyloxy group, 4-hydroxybutyloxy group, 2-mercaptoethyloxy group, 3-mercapto propyloxy group, 4-mercapto butyloxy group, 2-amino ethyloxy group, 3-aminopropyloxy group, 4-aminobutyloxy group, benzyloxy group, 2-phenethyloxy group, 3-phenylpropyloxy group, 5-hydroxymethyl-3-pyridylmethyloxy group, 5-acetoxymethyl-3-pyridylmethyloxy group, 6-hydroxymethyl-2-pyridylmethyloxy group, 6-acetoxymethyl-2-pyridyl methyloxy group, 5-methyl-3-pyridylmethyloxy group, 6-methyl-2-pyridylmethyloxy group, 5-ethyl-3-pyridylmethyloxy group, 5-t-butyl-3-pyridylmethyloxy group, 5-methoxycarbonyl-3-pyridylmethyloxy group, 5-ethoxycarbonyl-3-pyridylmethyloxy group, 2-pyrazinyl methyloxy group, 2-pyrimidinyl methyloxy group, 4-pyrimidinyl methyloxy group, 5-pyrimidinyl methyloxy group, 2-furyl methyloxy group, 3-furyl methyloxy group, 2-thienylmethyloxy group, 3-thienylmethyloxy group, 3-oxadiazolyl

methyloxy group, 2-(4-methoxy phenoxy) ethyloxy group, 3-(4-methoxyphenoxy) propyloxy group, 4-(4-methoxyphenoxy) butyloxy group and the like.

Preferably the substitution site for R^1 is the 2-position, and preferably R^1 denotes a hydroxy group, methoxy group, carboxymethyloxy group, 2-carboxyethyloxy group, 3-carboxypropyloxy group, methoxycarbonylmethyloxy group, ethoxycarbonylmethyloxy group, n-propoxy carbonyl methyloxy group, i-propoxy carbonyl methyloxy group, n-butoxycarbonyl methyloxy group, t-butoxycarbonyl methyloxy group, N-hydroxymethyl carbamoylmethyloxy group, N-ethyl carbamoylmethyloxy group, 4-hydroxy-2-oxobutyloxy group, 5-hydroxy-2-oxo pentyloxy group, 2-hydroxyethyloxy group, 3-hydroxy propyloxy group, 4-hydroxybutyloxy group, 3-aminopropyloxy group, 4-aminobutyloxy group, benzyloxy group, 5-hydroxymethyl-3-pyridylmethyloxy group, 5-acetoxymethyl-3-pyridylmethyloxy group, 6-hydroxymethyl-2-pyridylmethyloxy group, 6-acetoxymethyl-2-pyridylmethyloxy group, 5-methyl-3-pyridyl methyloxy group, 6-methyl-2-pyridyl methyloxy group, 2-pyridylmethyloxy group, 3-pyridylmethyloxy group, 4-pyridylmethyloxy group, 2-pyrazinyl methyloxy group, 2-pyrimidinyl methyloxy group, 4-pyrimidinyl methyloxy group or 5-pyrimidinyl methyloxy group.

More preferably, R^1 denotes a hydroxy group, methoxy group, carboxymethyloxy group, 2-carboxyethyloxy group, 3-carboxypropyloxy group, N-hydroxy methylcarbamoyl methyloxy group, N-ethyl carbamoylmethyloxy group, 4-hydroxy-2-oxo butyloxy group, 5-hydroxy-2-oxo pentyloxy group, 2-hydroxyethyloxy group, 3-hydroxy propyloxy group, 4-hydroxy butyloxy group, benzyloxy group, 2-pyridylmethyloxy group, 3-pyridylmethyloxy group, 4-pyridyl methyloxy group, 2-pyrazinyl methyloxy group, 2-pyrimidinyl methyloxy group, 4-pyrimidinyl methyloxy group or 5-pyrimidinyl methyloxy group.

Moreover, in the formula, R^2 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, 4-morpholyl acetyl group, 1-4C straight or branched chain alkanoyloxy group, 1-4C straight or branched chain alkanoyl group, 1-4C straight or branched chain alkyl group, 1-3C alkylthio group optionally mono-substituted by a group arbitrarily selected from the group comprising an hydroxy group, carboxyl group, phenyl group and pyridyl group or 1-4C straight or branched chain alkoxy group optionally substituted by one alkoxycarbonyl group of carbon number 1-4.

More precisely wherein halogen atom denotes a fluorine atom, chlorine atom or bromine atom; optionally protected hydroxy group denotes a hydroxy group, trimethylsilyloxy group, t-butyldimethylsilyloxy group, methoxymethyloxy group or the like; optionally protected mercapto group denotes a phenylthio group, benzylthio group or the like; 1-4C straight or branched chain alkanoyloxy group denotes an acetoxy group, propionyloxy group, butyryloxy group, pivaloyloxy group or the like; 1-4C straight or branched chain alkanoyl group denotes an acetyl group, propionyl group, pivaloyl group or the like; 1-4C alkyl group denotes a methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, t-butyl group or the like; 1-3C alkylthio group optionally mono-substituted by a group arbitrarily selected from the group comprising hydroxy group, carboxyl group, phenyl group or pyridyl group denotes methylthio group, ethylthio group, 3-hydroxypropyl thio group, carboxymethyl thio group, 3-pyridylmethyl thio group or the like; 1-4C straight or branched chain alkoxy group optionally substituted by one 1-4C alkoxycarbonyl group denotes a methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butoxy group, t-butoxy group, methoxycarbonylmethyloxy group, ethoxycarbonylmethyloxy group, n-propoxy carbonyl methyloxy group, i-propoxy carbonyl methyloxy group, n-butoxycarbonyl methyloxy group, t-butoxycarbonyl methyloxy group, 2-(methoxycarbonyl) ethyloxy group, 2-(ethoxycarbonyl) ethyloxy group, 2-(n-propoxy carbonyl) ethyloxy group, 2-(i-propoxy carbonyl) ethyloxy group, 2-(n-butoxycarbonyl) ethyloxy group, 2-(t-butoxycarbonyl) ethyloxy group, 2-(n-pentyloxy carbonyl) ethyloxy group, 3-(methoxycarbonyl) propyloxy group, 3-(ethoxycarbonyl) propyloxy group, 3-(n-propoxy carbonyl) propyloxy group, 3-(i-propoxy carbonyl) propyloxy group, 3-(n-butoxy carbonyl) propyloxy group, 3-(t-butoxycarbonyl) propyloxy group or the like.

Preferably the substitution site of R^2 is the 9 or 10-position, and R^2 preferably denotes a hydrogen atom, hydroxy group, fluorine atom, chlorine atom, bromine atom, methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butoxy group, t-butoxy group or trifluoromethyl group.

More preferably, the substitution site of R^2 is the 9-position and R^2 denotes a chlorine atom, bromine atom or trifluoromethyl group.

Moreover, in the formula, R^3 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group or 1-4C straight or branched chain alkoxy group. More precisely wherein halogen atom denotes a fluorine atom, chlorine atom, bromine atom or the like; optionally protected hydroxy group denotes a hydroxy group, trimethylsilyloxy group, t-butyldimethylsilyloxy group,

methoxymethyloxy group or the like; and 1-4C straight or branched chain alkoxy group denotes a methoxy group, ethoxy group, n-propoxy group, i-propoxy group, cyclo propoxy group, n-butoxy group, t-butoxy group or the like.

Preferably R^3 denotes a hydrogen atom, hydroxy group, fluorine atom, chlorine atom, bromine atom, methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butoxy group, t-butoxy group. More preferably, R^3 denotes a hydrogen atom.

Preferably R^2 and R^3 are not both hydrogen atoms.

As far as combinations of R^2 and R^3 are concerned, preferably the substitution site of R^2 is the 9 or 10-position, and R^2 is a hydrogen atom, halogen atom, hydroxy group, trifluoromethyl group or 1-4C straight or branched chain alkoxy group and R^3 is a hydrogen atom. Further more preferably, R^2 is a halogen atom or trifluoromethyl group substituted at the 9-position and R^3 is a hydrogen atom.

Moreover, in the formula, R^4 denotes a hydrogen atom, halogen atom, optionally protected carboxyl group, phenoxy group, anilino group, N-methylanilino group, 4-morpholyl carbonyl group, alkyl group of carbon number 1 or 2 optionally substituted by a 3-6C cyclic alkyl group, benzyl group optionally mono- or di-substituted on the phenyl moiety by 1 or 2 members arbitrarily selected from the group comprising a halogen atom, hydroxy group, mercapto group, alkoxy group of carbon number 1 or 2, alkylthio group of carbon number 1 or 2, 1-4C alkoxycarbonyl group, acetylamino group, carboxyl group and amino group, pyridylmethyl group optionally substituted by a 1-4C alkyl group, morpholyl methyl group, triazolyl methyl group, furyl methyl group, thienylmethyl group, pyrimidinyl methyl group, pyrazinyl methyl group, pyrrolylmethyl group, imidazolylmethyl group, quinolyl methyl group, indolyl methyl group, naphthylmethyl group, benzoyl group, α-hydroxybenzyl group or alkoxycarbonyl group of carbon number 1 or 2.

More precisely wherein halogen atom denotes a fluorine atom, chlorine atom or bromine atom; alkyl group of carbon number 1 or 2 optionally substituted by a 3-6C cyclic alkyl group denotes a methyl group, ethyl group, cyclopropylmethyl group, cyclohexylmethyl group or the like; benzyl group optionally mono- or di-substituted on the phenyl moiety by 1 or 2 members arbitrarily selected from the group comprising a halogen atom, hydroxy group, mercapto group, alkoxy group of carbon number 1 or 2, alkylthio group of carbon number 1 or 2, 1-4C alkoxycarbonyl group, acetylamino

group, carboxyl group and amino group denotes a 2-fluorobenzyl group, 2-chlorobenzyl group, 2-bromobenzyl group, 3-fluorobenzyl group, 3-chlorobenzyl group, 3-bromobenzyl group, 4-fluorobenzyl group, 4-chlorobenzyl group, 4-bromobenzyl group, 2-hydroxybenzyl group, 3-hydroxybenzyl group, 4-hydroxybenzyl group, 2-mercapto benzyl group, 3-mercapto benzyl group, 4-mercapto benzyl group, 2-methoxybenzyl group, 3-methoxybenzyl group, 4-methoxybenzyl group, 2-ethoxy benzyl group, 3-ethoxy benzyl group, 4-ethoxy benzyl group, 2-methylthio benzyl group, 3-methylthio benzyl group, 4-methylthio benzyl group, 2-ethylthio benzyl group, 3-ethylthio benzyl group, 4-ethylthio benzyl group, 2-methoxycarbonyl benzyl group, 3-methoxycarbonyl benzyl group, 4-methoxycarbonyl benzyl group, 2-ethoxy carbonyl benzyl group, 3-ethoxycarbonyl benzyl group, 4-ethoxycarbonyl benzyl group, 2-t-butoxy carbonyl benzyl group, 3-t-butoxycarbonyl benzyl group, 4-t-butoxycarbonyl benzyl group, 2-acetylamino benzyl group, 3-acetylamino benzyl group, 4-acetylamino benzyl group, 2-carboxy benzyl group, 3-carboxy benzyl group, 4-carboxy benzyl group, 2-aminobenzyl group, 3-aminobenzyl group, 4-aminobenzyl group, 2,3-difluoro benzyl group, 2,4-difluoro benzyl group, 2,5-difluoro benzyl group, 3,4-difluoro benzyl group, 3,5-difluoro benzyl group, 2,3-dichloro benzyl group, 2,4-dichloro benzyl group, 2,5-dichloro benzyl group, 3,4-dichloro benzyl group, 3,5-dichloro benzyl group, 2,3-dibromo benzyl group, 2,4-dibromo benzyl group, 2,5-dibromo benzyl group, 3,4-dibromo benzyl group, 3,5-dibromo benzyl group, 2,3-dihydroxy benzyl group, 2,4-dihydroxy benzyl group, 2,5-dihydroxy benzyl group, 3,4-dihydroxy benzyl group, 3,5-dihydroxy benzyl group, 2,3-dimethoxybenzyl group, 2,4-dimethoxybenzyl group, 2,5-dimethoxybenzyl group, 3,4-dimethoxybenzyl group, 3,5-dimethoxybenzyl group, 2,3-diethoxy benzyl group, 2,4-diethoxy benzyl group, 2,5-diethoxy benzyl group, 3,4-diethoxy benzyl group, 3,5-diethoxy benzyl group, 2-fluoro-3-methoxy benzyl group, 2-fluoro-4-methoxybenzyl group, 2-fluoro-5-methoxybenzyl group, 3-fluoro-4-methoxybenzyl group, 3-fluoro-5-methoxybenzyl group, 3-fluoro-2-methoxybenzyl group, 4-fluoro-2-methoxybenzyl group, 5-fluoro-2-methoxybenzyl group, 4-fluoro-3-methoxybenzyl group, 5-fluoro-3-methoxybenzyl group or the like; pyridyl methyl group optionally substituted by a 1-4C alkyl group denotes a 2-pyridylmethyl group, 3-pyridylmethyl group, 4-pyridylmethyl group, 5-methyl-3-pyridylmethyl group, 6-methyl-2-pyridylmethyl group or the like; and alkoxycarbonyl group of carbon number 1 or 2 denotes a methoxy carbonyl group, ethoxy carbonyl group or the like.

Preferably R^4 denotes a hydrogen atom, methyl group, 2-pyrimidinyl methyl group, 4-pyrimidinyl methyl group, 5-pyrimidinyl methyl group, 2-pyridylmethyl group, 3-pyridylmethyl group, 4-pyridylmethyl group, 5-methyl-3-pyridylmethyl group or 6-methyl-2-pyridylmethyl group.

More preferably, R^4 denotes a methyl group, 5-pyrimidinyl methyl group, 2-pyridylmethyl group, 3-pyridylmethyl group or 4-pyridylmethyl group.

Moreover, in the formula, R^5 denotes a hydrogen atom or methyl group, and preferably a hydrogen atom.

Moreover, in the formula, when R^1, R^2, R^3 and R^5 are simultaneously hydrogen atoms, R^4 is a substituent other than a hydrogen atom, benzyl group, 4-diethylamino benzyl group or furyl methyl group.

As combinations of substituents, preferably, the substitution site for R^1 is the 2-position and R^1 is a hydroxy group, carboxymethyloxy group, 2-carboxyethyloxy group, 3-carboxypropyloxy group, N-hydroxymethyl carbamoylmethyloxy group, N-ethyl carbamoylmethyl oxo group, 4-hydroxy-2-oxobutyloxy group, 5-hydroxy-2-oxo pentyloxy group, 2-hydroxyethyloxy group, 3-hydroxy propyloxy group, 4-hydroxy butyloxy group, benzyloxy group, 2-pyridino methyloxy group, 3-pyridino methyloxy group, 4-pyridino methyloxy group, 2-pyrazinyl methyloxy group, 2-pyrimidinyl methyloxy group, 4-pyrimidinyl methyloxy group or 5-pyrimidinyl methyloxy group; R^2 is a chlorine atom, bromine atom or trifluoromethyl group substituted in the 9-position; R^3 is a hydrogen atom; R^4 is a methyl group, 5-pyrimidinyl methyl group, 2-pyridylmethyl group, 3-pyridylmethyl group or 4-pyridylmethyl group; and R^5 is a hydrogen atom.

Moreover, in formula (IV), R^6 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, 1-4C alkoxycarbonyl group, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, optionally protected hydroxy group, optionally protected mercapto group, 1-4C straight or branched chain alkyl group optionally substituted by one hydroxy group, amino group optionally mono- or di-substituted by a 1-4C alkyl group, 1-3C alkylthio group or 1-6C straight chain alkoxy group optionally substituted by a 4-methoxyphenoxy group; R^7 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, 1-4C straight or branched chain alkanoyl group, 1-4C straight or branched chain alkyl group or 1-4C straight or branched chain alkoxy group; R^8 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group or 1-4C straight or branched chain alkoxy group; and R^{10} denotes a

hydrogen atom, halogen atom, phenoxy group, α-hydroxybenzyl group, anilino group, N-methylanilino group, methyl group or halogenomethyl group. More precisely, the definitions for each embodying substituent are as described in greater detail for the corresponding substituents described for R^1, R^2, R^3 and R^4 in formula (I).

Moreover, in formula (XVI) in accordance with the later-described process for production, R^9 denotes a hydrogen or methyl group, and R^{11} denotes a hydrogen or straight or branched chain alkyl group of carbon number 1-4, wherein more precisely by straight or branched chain alkyl group of carbon number 1-4, there is meant a methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, t-butyl group and the like.

Moreover, R^{12} in formula (XIX) denotes a hydrogen atom, methyl group, 3-6C cyclic alkyl group, phenyl group which may be mono- or di-substituted by 1 or 2 members arbitrarily selected from the group comprising a halogen atom, hydroxy group, mercapto group, alkoxy group of carbon number 1 or 2, alkylthio group of carbon number 1 or 2, 1-4C alkoxycarbonyl group, acetylamino group, carboxyl group and amino group, pyridyl group optionally substituted by a 1-4C alkyl group, morpholyl group, triazolyl group, furyl group, thienyl group, pyrimidinyl group, pyrazinyl group, pyrrolyl group, imidazolyl group, quinolyl group, indolyl group or naphthyl group.

More precisely, 3-6C cyclic alkyl group denotes a cyclopropyl group, cyclohexyl group or the like; phenyl group optionally mono- or di-substituted by 1 or 2 members arbitrarily selected from the group comprising a halogen atom, hydroxy group, mercapto group, 1-2C alkoxy group, alkylthio group of carbon number 1 or 2, 1-4C alkoxycarbonyl group, acetylamino group, carboxyl group and amino group, denotes a 2-fluorophenyl group, 2-chlorophenyl group, 2-bromo phenyl group, 3-fluorophenyl group, 3-chlorophenyl group, 3-bromo phenyl group, 4-fluorophenyl group, 4-chlorophenyl group, 4-bromo phenyl group, 2-hydroxyphenyl group, 3-hydroxyphenyl group, 4-hydroxyphenyl group, 2-mercaptophenyl group, 3-mercaptophenyl group, 4-mercaptophenyl group, 2-methoxyphenyl group, 3-methoxyphenyl group, 4-methoxyphenyl group, 2-ethoxyphenyl group, 3-ethoxyphenyl group, 4-ethoxyphenyl group, 2-n-propoxy phenyl group, 3-n-propoxy phenyl group, 4-n-propoxy phenyl group, 2-i-propoxy phenyl group, 3-i-propoxy phenyl group, 4-i-propoxy phenyl group, 2-n-butoxy phenyl group, 3-n-butoxy phenyl group, 4-n-butoxy phenyl group, 2-t-butoxy phenyl group, 3-t-butoxy phenyl group, 4-t-butoxy phenyl group, 2-methoxycarbonyl phenyl group, 3-methoxycarbonyl phenyl group, 4-methoxycarbonyl phenyl

group, 2-ethoxycarbonyl phenyl group, 3-ethoxycarbonyl phenyl group, 4-ethoxycarbonyl phenyl group, 2-t-butoxycarbonyl phenyl group, 3-t-butoxycarbonyl phenyl group, 4-t-butoxycarbonyl phenyl group, 2-acetylaminophenyl group, 3-acetylaminophenyl group, 4-acetylaminophenyl group, 2-carboxy phenyl group, 3-carboxy phenyl group, 4-carboxy phenyl group, 2-aminophenyl group, 3-aminophenyl group, 4-aminophenyl group, 2,3-difluorophenyl group, 2,4-difluorophenyl group, 2,5-difluorophenyl group, 3,4-difluorophenyl group, 3,5-difluorophenyl group, 2,3-dichloro phenyl group, 2,4-dichloro phenyl group, 2,5-dichloro phenyl group, 3,4-dichloro phenyl group, 3,5-dichloro phenyl group, 2,3-dibromo phenyl group, 2,4-dibromo phenyl group, 2,5-dibromo phenyl group, 3,4-dibromo phenyl group, 3,5-dibromo phenyl group, 2,3-dihydroxyphenyl group, 2,4-dihydroxyphenyl group, 2,5-dihydroxyphenyl group, 3,4-dihydroxyphenyl group, 3,5-dihydroxyphenyl group, 2,3-dimethoxyphenyl group, 2,4-dimethoxy phenyl group, 2,5-dimethoxyphenyl group, 3,4-dimethoxyphenyl group, 3,5-dimethoxyphenyl group, 2,3-diethoxy phenyl group, 2,4-diethoxy phenyl group, 2,5-diethoxy phenyl group, 3,4-diethoxy phenyl group, 3,5-diethoxy phenyl group, 2-fluoro-3-methoxyphenyl group, 2-fluoro-4-methoxyphenyl group, 2-fluoro-5-methoxyphenyl group, 3-fluoro-4-methoxyphenyl group, 3-fluoro-5-methoxyphenyl group, 3-fluoro-2-methoxyphenyl group, 4-fluoro-2-methoxyphenyl group, 5-fluoro-2-methoxyphenyl group, 4-fluoro-3-methoxyphenyl group, 5-fluoro-3-methoxyphenyl group and the like; and pyridyl group optionally substituted by a 1-4C alkyl group denotes a 2-pyridyl group, 3-pyridyl group, 4-pyridyl group, 5-methyl-3-pyridyl group, 6-methyl-2-pyridyl group and the like. Preferably, R^{12} denotes a 2-pyrimidinyl group, 4-pyrimidinyl group, 5-pyrimidinyl group, 2-pyridyl group, 3-pyridyl group, 4-pyridyl group, 5-methyl-3-pyridyl group or 6-methyl-2-pyridyl group. More preferably, R^{12} denotes a 5-pyrimidinyl group, 2-pyridyl group, 3-pyridyl group or 4-pyridyl group.

Moreover, R^{13} in formula (XX) denotes a 1-4C alkoxy carbonyl group, 3-carboxy-1-propenyl group, 2,2-diethoxy ethyl group, 1-4C straight or branched chain alkanoyl group, carbonyl group substituted by a phenyl group or pyridyl group or a group: $-(CH_2)_n-Z$ (Z denotes a hydrogen atom, carboxyl group, alkoxy group of carbon number 1 or 2 optionally substituted by one hydroxy group, 1-6C alkoxycarbonyl group, carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or 1-2C alkyl group, alkanoyl group of carbon number 1 to 4 optionally substituted by one hydroxy group or mercapto group, piperidinyl carbonyl group optionally substituted by one carboxyl group or 1-2C alkoxycarbonyl group, morpholyl carbonyl group, hydroxy group, mercapto group, amino group, phenyl group, pyridyl group optionally mono-substituted by a hydroxymethyl group,

acetoxymethyl group, 1-4C alkyl group or 1-2C alkoxycarbonyl group, pyrazinyl group, pyrimidinyl group, furyl group, thienyl group, oxadiazolyl group or 4-methoxyphenoxy group, and n denotes 1-6).

More precisely, 1-4C alkoxycarbonyl group denotes a methoxycarbonyl group, ethoxycarbonyl group, n-propoxy carbonyl group, i-propoxy carbonyl group, cyclo propoxy carbonyl group, n-butoxycarbonyl group, t-butoxycarbonyl group or the like; straight or branched chain alkanoyl group of carbon number 1-4 denotes an acetyl group, propionyl group, butyryl group, pivaloyl group or the like; carbonyl group substituted by a phenyl group or pyridyl group denotes a benzoyl group, nicotinoyl group, isonicotinoyl group or the like; and a group $-(CH_2)_n-Z$ (Z denotes a hydrogen atom, carboxyl group, alkoxy group of carbon number 1 or 2 optionally substituted by one hydroxy group, 1-6C alkoxycarbonyl group, carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or 1-2C alkyl group, alkanoyl group of carbon number 1 to 4 optionally substituted by one hydroxy group or mercapto group, piperidinyl carbonyl group optionally substituted by one carboxyl group or 1-2C alkoxycarbonyl group, morpholyl carbonyl group, hydroxy group, mercapto group, amino group, phenyl group, pyridyl group optionally mono-substituted by a hydroxymethyl group, acetoxymethyl group, 1-4C alkyl group or 1-2C alkoxycarbonyl group, pyrazinyl group, pyrimidinyl group, furyl group, thienyl group, oxadiazolyl group or 4-methoxyphenoxy group, and n denotes 1-6) denotes a methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, t-butyl group, n-pentyl group, n-hexyl group, carboxymethyl group, 2-carboxyethyl group, 3-carboxypropyl group, methoxy methyl group, ethoxymethyl group, 2-methoxyethyl group, 2-ethoxyethyl group, 2-(2-hydroxyethoxy) ethyl group, methoxycarbonyl methyl group, ethoxycarbonyl methyl group, n-propoxy carbonyl methyl group, i-propoxy carbonyl methyl group, n-butoxycarbonyl methyl group, t-butoxycarbonyl methyl group, n-pentyloxy carbonyl methyl group, n-hexyloxy carbonyl methyl group, cyclopropyloxycarbonyl methyl group, cyclohexyloxy carbonyl methyl group, 2-(methoxycarbonyl) ethyl group, 2-(ethoxycarbonyl) ethyl group, 2-(n-propoxy carbonyl) ethyl group, 2-(i-propoxy carbonyl) ethyl group, 2-(n-butoxycarbonyl) ethyl group, 2-(t-butoxy carbonyl) ethyl group, 2-(n-pentyloxy carbonyl) ethyl group, 2-(n-hexyloxy carbonyl) ethyl group, 2-(cyclopropyloxycarbonyl) ethyl group, 2-(cyclohexyloxycarbonyl) ethyl group, 3-(methoxycarbonyl) propyl group, 3-(ethoxycarbonyl) propyl group, 3-(n-propoxy carbonyl) propyl group, 3-(i-propoxy carbonyl) propyl group, 3-(n-butoxy carbonyl) propyl group, 3-(t-butoxycarbonyl) propyl group, 3-(n-pentyloxy carbonyl) propyl group, 3-(n-hexyloxy carbonyl) propyl group, 3-

(cyclopropyloxycarbonyl) propyl group, 3-(cyclohexyloxy carbonyl) propyl group, N-hydroxymethyl carbamoylmethyl group, N-methylcarbamoyl methyl group, N,N-dimethylcarbamoylmethyl group, N-ethyl carbamoylmethyl group, N,N-diethylcarbamoyl methyl group, N-n-propyl carbamoylmethyl group, N-n-butyl carbamoylmethyl group, 3-hydroxy-2-oxopropyl group, 4-hydroxy-3-oxobutyl group, 5-hydroxy-4-oxo pentyl group, 4-hydroxy-2-oxobutyl group, 5-hydroxy-2-oxopentyl group, 6-hydroxy-2-oxohexyl group, 5-mercapto-2-oxopentyl group, 4-carboxy-1-piperidinyl carbonyl methyl group, 4-methoxycarbonyl-1-piperidinyl carbonyl methyl group, 4-ethoxycarbonyl-1-piperidinyl carbonyl methyl group, 4-morpholyl carbonyl methyloxy group, 2-hydroxy ethyl group, 3-hydroxypropyl group, 4-hydroxybutyl group, 2-mercaptoethyl group, 3-mercapto propyl group, 4-mercapto butyl group, 2-amino ethyl group, 3-aminopropyl group, 4-aminobutyl group, benzyl group, 2-phenethyl group, 3-phenylpropyl group, 5-hydroxymethyl-3-pyridylmethyl group, 5-acetoxymethyl-3-pyridylmethyl group, 6-hydroxymethyl-2-pyridylmethyl group, 6-acetoxymethyl-2-pyridylmethyl group, 5-methyl-3-pyridylmethyl group, 6-methyl-2-pyridylmethyl group, 5-ethyl-3-pyridylmethyl group, 5-t-butyl-3-pyridylmethyl group, 5-methoxycarbonyl-3-pyridylmethyl group, 5-ethoxy carbonyl-3-pyridylmethyl group, 2-pyrazinyl methyl group, 2-pyrimidinyl methyl group, 4-pyrimidinyl methyl group, 5-pyrimidinyl methyl group, 2-furyl methyl group, 3-furyl methyl group, 2-thienylmethyl group, 3-thienylmethyl group, 3-oxadiazolyl methyl group, 2-(4-methoxyphenoxy) ethyl group, 3-(4-methoxyphenoxy) propyl group or 4-(4-methoxyphenoxy) butyl group.

Preferably R^{13} denotes a carboxymethyl group, 2-carboxyethyl group, 3-carboxypropyl group, methoxycarbonylmethyl group, ethoxycarbonylmethyl group, n-propoxy carbonyl methyl group, i-propoxy carbonyl methyl group, n-butoxycarbonyl methyl group, t-butoxycarbonyl methyl group, N-hydroxymethyl carbamoylmethyl group, N-ethyl carbamoylmethyl group, 4-hydroxy-2-oxobutyl group, 5-hydroxy-2-oxo pentyl group, 2-hydroxyethyl group, 3-hydroxypropyl group, 4-hydroxybutyl group, 3-aminopropyl group, 4-aminobutyl group, benzyl group, 5-hydroxymethyl-3-pyridylmethyl group, 5-acetoxymethyl-3-pyridylmethyl group, 6-hydroxymethyl-2-pyridyl methyl group, 6-acetoxymethyl-2-pyridylmethyl group, 5-methyl-3-pyridylmethyl group, 6-methyl-2-pyridylmethyl group, 2-pyridyl methyl group, 3-pyridylmethyl group, 4-pyridylmethyl group, 2-pyrazinyl methyl group, 2-pyrimidinyl methyl group, 4-pyrimidinyl methyl group or 5-pyrimidinyl methyl group.

More preferably, R^{13} denotes a carboxymethyl group, 2-carboxyethyl group, 3-carboxypropyl group,

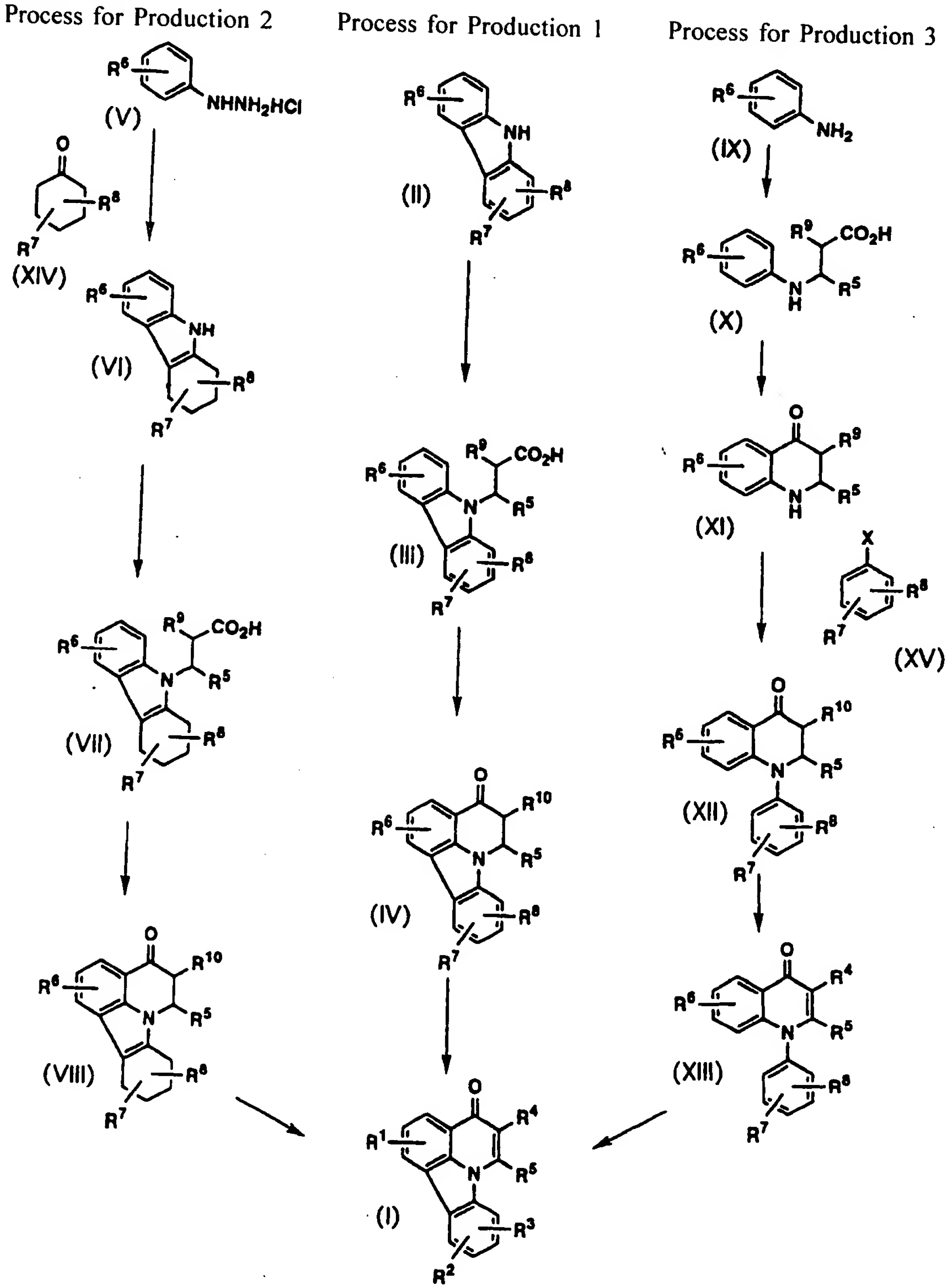
N-hydroxymethyl carbamoylmethyl group, N-ethyl carbamoylmethyl group, 4-hydroxy-2-oxo butyl group, 5-hydroxy-2-oxo pentyl group, 2-hydroxyethyl group, 3-hydroxypropyl group, 4-hydroxybutyl group, benzyl group, 2-pyridylmethyl group, 3-pyridylmethyl group, 4-pyridylmethyl group, 2-pyrazinyl methyl group, 2-pyrimidinyl methyl group, 4-pyrimidinyl methyl group or 5-pyrimidinyl methyl group. In this specification, by carbon number in the case of an alkoxycarbonyl group, alkanoyloxy group or alkanoyl group, there is respectively meant the carbon number of the alkoxy moiety, alkyl moiety or alkyl moiety.

In this specification, as protecting groups for optionally protected substituents, other than when specifically stated, as protecting groups for hydroxy groups, alkyl type protecting groups such as for example a methyl group, t-butyl group, benzyl group, trityl group, methoxy methyl group and the like, silyl type protecting groups such as for example a trimethylsilyl group, t-butyldimethylsilyl group and the like, acyl type protecting groups such as for example a formyl group, acetyl group, benzoyl group and the like, carbonate type protecting groups such as for example a methoxycarbonyl group, benzyloxycarbonyl group and the like may be proposed. As protecting groups for carboxyl groups, ester type protecting groups such as for example methyl group, ethyl group, t-butyl group, benzyl group, methoxy methyl group and the like may be proposed. As protecting groups for amino groups, alkyl type protecting groups such as for example benzyl group, trityl group, methoxy methyl group and the like, acyl type protecting groups such as for example formyl group, acetyl group, benzoyl group and the like, carbamate protecting groups and the like such as for example t-butoxy carbonyl group, benzyloxycarbonyl group and the like may be proposed.

The compounds of this invention can form salts with inorganic acids or organic acids. Examples of these salts include salts with inorganic acid such as hydrochlorides, sulfates, nitrates and the like, salts with organic acids such as acetates, oxalates, maleates, tartrates, p-toluenesulfonates, methanesulfonates and the like. Also, salts with organic bases or inorganic bases can be formed depending on the species of substituents. Examples of salts with inorganic bases include salts with sodium carbonate, potassium carbonate and the like, and examples of salts with organic bases include salts with triethylamine, diethylamine, pyridine and the like. Such salts can be obtained by conventional methods, for example an equivalent quantity of a compound of this invention and a solution including the desired acid or base may be mixed together, and the desired salt recovered by filtration or elimination of the solvent by distillation.

The compounds of this invention represented by formula (I) can be obtained using a process for production represented by the following reaction equation. The definitions of Reaction Equation 1 and Reaction Equation 2, and the compounds represented by formula (I), formula (II), formula (III), formula (IV), formula (V), formula (VI), formula (VII), formula (VIII), formula (IX), formula (X), formula (XI), formula (XII), formula (XIII), formula (XIV), formula (XV), formula (XVI), formula (XVII), formula (XVIII), formula (XIX), formula (XX), formula (XXI), formula (XXII), formula (XXIII) and formula (XXIV) in explanation, and furthermore R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, X and Z of in the formulae are the same as in the aforesaid definitions. In the synthesis of pyridocarbazole derivatives exemplified by formula (I) which are compounds of this invention and salts thereof, these can be produced using Process for Production 1 of Reaction Equation 1 from the compound represented by formula (II), formula (V) or formula (IX) or salts thereof which can be readily produced in accordance with well-known literature or are commercial compounds. Moreover, the said derivatives can be also produced using Process for Production 2 or Process for Production 3.

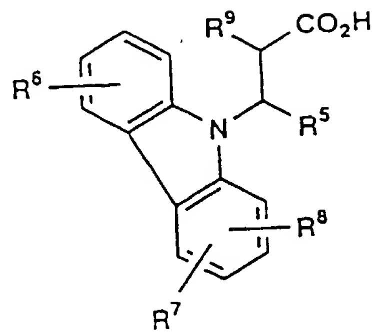
Reaction Equation 1



Hereinafter, the processes for production will be described in greater detail.

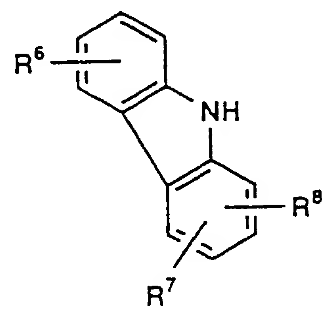
Process for Production 1

A compound represented by the following formula (III)



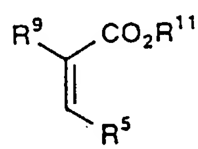
(III)

can be obtained by reacting a carbazole derivative represented by formula (II)



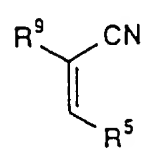
(II)

or a salt thereof with a compound represented by following formula (XVI)



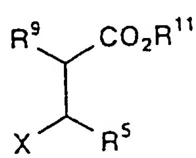
(XVI)

or following formula (XVII)



(XVII)

or following formula (XVIII)



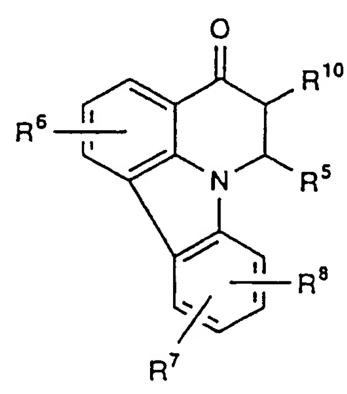
(XVIII)

and by hydrolysing in accordance with requirements.

In other words, a compound of formula (III) can be obtained by a procedure wherein, a Michael addition reaction is carried out between a compound of formula (II) and a compound of formula (XVI) or formula (XVII) in the co-presence or absence of copper acetate, N-benzyl trimethyl ammonium hydroxide (Triton B) or the like, but preferably in the presence of Triton B with a non-solvent or water, or a ketone system solvent such as for example acetone, methyl ethyl ketone or the like or an ether type solvent such as for example tetrahydrofuran (THF), dioxane, 1,2-dimethoxyethane (DME) or the like, but preferably using acetone as solvent, at from under ice-cooling to a temperature at which the reaction mixture boils under reflux, but preferably at room temperature, for sufficient time for the reaction to proceed, for example 15 minutes to 1 hour, and carrying out hydrolysis in accordance with requirements in an acidic aqueous solution such as for example diluted hydrochloric acid, dilute sulfuric acid or the like or basic aqueous solution such as for example dilute sodium hydroxide aqueous solution, dilute potassium hydroxide or the like, but preferably in dilute hydrochloric acid aqueous solution or dilute sodium hydroxide aqueous solution, at from room temperature to a temperature at which the reaction mixture boils under reflux, and more preferably at room temperature, for sufficient time for the reaction to proceed, for example 15 minutes to 12 hours;

or a procedure wherein an addition reaction is carried out between a compound of formula (II) and a compound of formula (XVIII) using an inorganic base such as for example potassium carbonate, cesium carbonate, calcium carbonate, sodium hydride or the like or organic base such as for example triethylamine, pyridine, N,N-dialkylaniline or the like, but preferably sodium hydride, and using as solvent, a polar solvent such as for example acetonitrile, dimethylformamide (DMF) or the like, a halogenated hydrocarbon solvent as exemplified by chloroform or methylene chloride or an ether type solvent as exemplified by ether, tetrahydrofuran (THF), but preferably DMF, at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably the temperature at which the reaction mixture boils under reflux, for a sufficient time for the reaction to proceed, for example for 15 minutes to 3 hours, and carrying out hydrolysis in accordance with requirements in an acidic aqueous solution such as for example diluted hydrochloric acid, dilute sulfuric acid or the like or basic aqueous solution such as for example dilute sodium hydroxide aqueous solution, dilute potassium hydroxide and the like, but preferably in dilute hydrochloric acid aqueous solution or dilute sodium hydroxide aqueous solution, at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at room temperature, for sufficient time for the reaction to proceed, for example 15 minutes to 12 hours.

Thereafter, the compound of formula (III) is formed into an acid halide using a thionyl halide reagent such as for example thionyl chloride or thionyl bromide and the like, with as solvent, a halogenated hydrocarbon solvent as exemplified by chloroform or methylene chloride, or aromatic hydrocarbon system solvent such as for example benzene, toluene or the like, but preferably methylene chloride, at from under ice-cooling to the temperature at which the reaction mixture boils under reflux, but preferably at room temperature, for sufficient time for the reaction to proceed, for example 15 minutes to 1 hour, and thereafter, a Friedel Krafts reaction is carried out without solvent or in nitrobenzene, carbon disulfide or in a halogenated hydrocarbon system solvent such as for example dichloromethane, carbon tetrachloride, 1,2-dichloroethane or the like, but preferably in carbon disulfide or methylene chloride as solvent, in the presence of a Lewis acid such as for example aluminum chloride, tin chloride, zinc chloride or the like, at -78°C to the temperature at which the reaction mixture boils under reflux, but preferably at room temperature, for sufficient time for the reaction to proceed, for example 15 minutes to 3 hours; or a reaction is carried out using anhydrous trifluoroacetic acid, in as solvent, an aromatic hydrocarbon system solvent such as for example benzene, toluene, xylene or the like, but preferably toluene, at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at the temperature of boiling under reflux, for sufficient time for the reaction to proceed, for example 3 hours to 10 hours; or a reaction is carried out in the presence of a phosphorus reagent such as for example phosphorus pentoxide, polyphosphoric acid or polyphosphoric acid ester or the like in the absence of solvent or in accordance with requirements, in an aromatic hydrocarbon system solvent such as for example benzene, toluene or the like, a halogenated hydrocarbon system solvent such as chlorobenzene, chloroform, methylene chloride or the like, but preferably in chloroform as solvent, at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at the temperature of boiling under reflux, for sufficient time for the reaction to proceed, for example 1 hour to 12 hours, and thereby the compound of following formula (IV)



(IV)

is obtained. As far as the selectivity of this ring closure reaction is concerned, ring closure will be

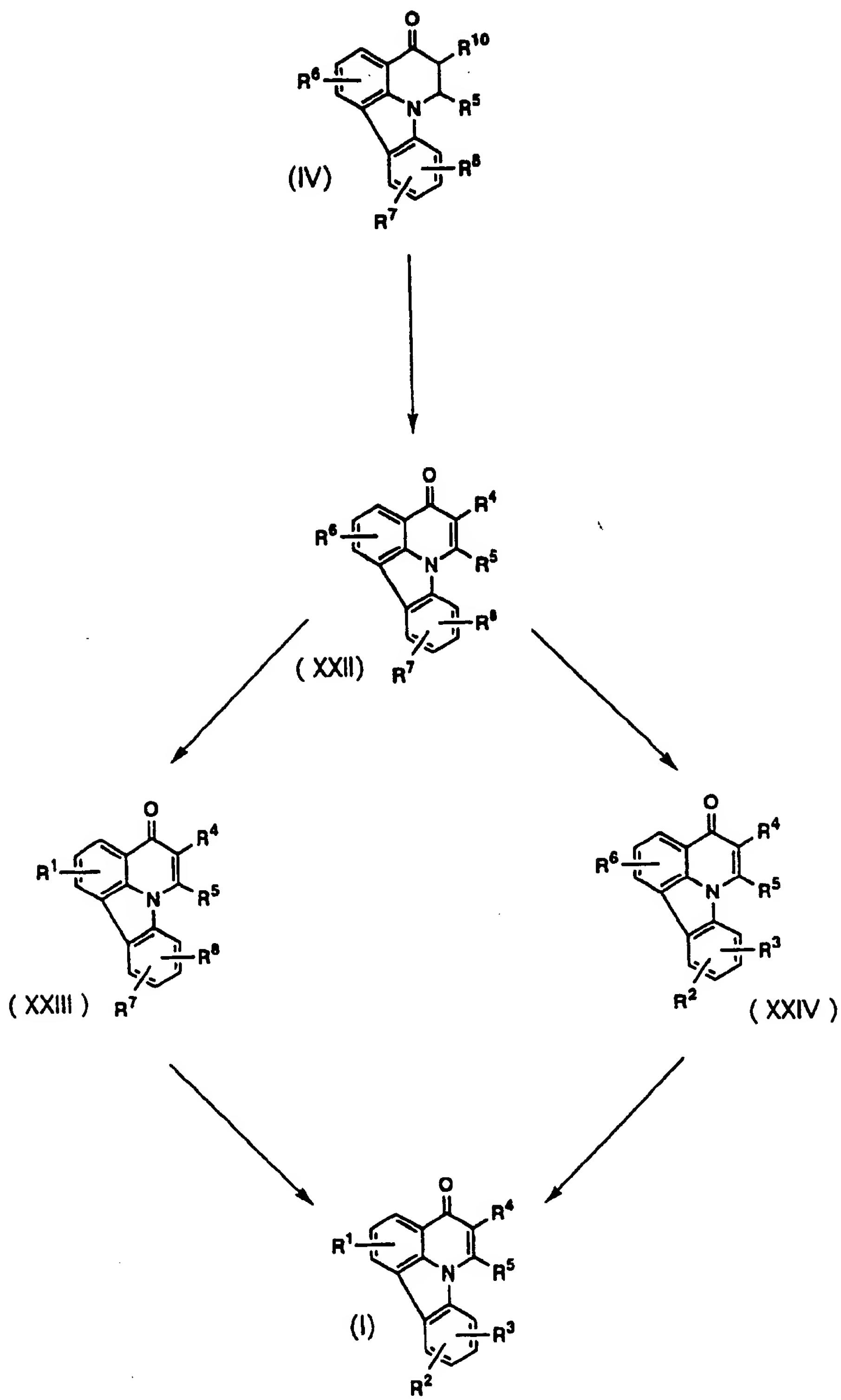
caused on the substituent side with the relatively large electron-donating properties in accordance with the differences in the electronic environments of substituents R^6 and R^7 (R^8) on the two benzene rings. In order to cause ring closure in the desired direction using this, a substituent which can be converted or eliminated after ring closure can be effectively used. Moreover, when ring closure selectivity is poor and a mixture is obtained, in accordance with requirements, separation and purification can be carried out by recrystallization or column chromatography or the like.

When R^6, R^7 and R^8 of the compound represented by formula (IV) are groups contained in R^1, R^2 and R^3 of the compound represented by formula (I), the compound of formula (IV) can be directly derived into the compound of formula (I) as shown in Process for Production 1 of Reaction Equation 1 by conversion of R^{10} to R^4 as described later.

Next, Reaction Equation 2 shows the substituent conversion when the compound represented by formula (IV) shown in Reaction Equation 1 is derived into the compound represented by formula (1), and this substituent conversion will now be described in greater detail.

Reaction Equation 2

Process for Production 1



The compound represented by formula (XXII) can be obtained from a compound of formula (IV) by the following reactions, namely,

an aldol condensation is carried out between a compound of formula (IV) and an aldehyde represented by R^{12}-CHO(XIX), in accordance with requirements in the presence of an inorganic base such as for example potassium hydroxide, sodium hydroxide, potassium carbonate or the like or organic base such as for example piperazine, piperidine, morpholine, n-BuLi or the like, but preferably in the presence of sodium hydroxide, using an alcohol system solvent such as for example methanol, ethanol or the like or an ether type solvent such as for example ether, THF, dioxane or the like, but preferably ethanol as solvent, at room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at room temperature, for sufficient time for the reaction to proceed, for example 3 hours to 12 hours, and the obtained compound, either without isolation is dehydrated within the reaction system and the double bond in the ring of the obtained enone isomerized or after isolation, is thereafter subjected to an oxidation (dehydrogenation) reaction using an oxidant such as for example chloranil, dichlorodicyanobenzoquinone (DDQ), 5 % palladium carbon or the like, but preferably DDQ and using as solvent, an aromatic hydrocarbon system non-polar solvent such as for example benzene, toluene, xylene or the like, an ether type solvent such as for example THF, DME, dioxane or the like, or an alcohol system solvent such as for example ethylene glycol or the like, but preferably dioxane, at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at room temperature, for sufficient time for the reaction to proceed, for example, 1 hour to 12 hours;

or a reaction derivative is formed by carrying out a halogenation in the absence or co-presence of light, and a peroxide such as benzoyl peroxide (BPO) or azo bis isobutyronitrile (AIBN) or the like, but preferably in the absence thereof, with the use of a suitable halogenating agent such as for example chlorine gas, bromine, cuprous bromide, N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), trihalogeno methane sulfonyl halide, trichloro bromomethane or the like, but preferably cuprous bromide, and the use as solvent of a halogenated hydrocarbon solvent such as for example carbon tetrachloride, chloroform, methylene chloride or the like, an aromatic hydrocarbon system non-polar solvent such as for example benzene, toluene or the like, acetic acid, carbon disulfide solvent, an ester solvent such as for example ethyl acetate or the like, but preferably chloroform or ethyl acetate, at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at the temperature of boiling under reflux for sufficient time for the reaction to proceed, for example 1 hour to 12 hours, and thereafter, a substitution reaction is carried out with phenol, aniline, N-methylaniline, triazole, imidazole, morpholine or the like using, in

accordance with requirements an inorganic base such as for example potassium carbonate, cesium carbonate, calcium carbonate or the like or an organic base such as for example triethylamine, pyridine, N,N-dialkylaniline or the like, but preferably cesium carbonate, and further in accordance with requirements, a polar solvent such as for example acetonitrile, dimethylformamide (DMF) or the like, a halogenated hydrocarbon solvent as exemplified by chloroform or methylene chloride, an ether type solvent as exemplified by ether or tetrahydrofuran (THF), but preferably in the absence of solvent, at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at room temperature, for sufficient time for the reaction to proceed, for example 30 minutes to 12 hours, and thereafter, an oxidation (dehydrogenation) reaction is carried out using an oxidant such as for example choranil, DDQ or the like, but preferably DDQ, and using as solvent, an aromatic hydrocarbon system non-polar solvent such as for example benzene, toluene, xylene or the like, an ether type solvent such as for example THF, DME, dioxane or the like, but preferably dioxane, at from room temperature to the temperature at which the reaction mixture boils under reflux, preferably at room temperature, for sufficient time for the reaction to proceed, for example 1 hour to 12 hours;

or an oxidation (dehydrogenation) reaction is carried out directly under the aforesaid conditions.

Thereafter, a substituent conversion is carried out in accordance with requirements. For example, the hydroxy body can be formed,

when R^6, R^7 or R^8 is a protected hydroxyl group, for example by deprotecting in hydrochloric acid aqueous solution or hydrofluoric acid aqueous solution, but preferably in hydrochloric acid aqueous solution, at from under ice cooling to the temperature at which the reaction mixture boils under reflux, but preferably at room temperature, for sufficient time for the reaction to proceed, for example 15 minutes to 12 hours;

or when R^6, R^7 or R^8 is a methoxy group, by deprotecting in the presence of boron tribromide, aluminum chloride or hydrobromic acid, but preferably in the presence of boron tribromide, using as solvent, a halogenated hydrocarbon system solvent such as for example methylene chloride, chloroform or the like or acetic acid solvent, but preferably methylene chloride, at from under ice cooling to the temperature at which the reaction mixture boils under reflux, but preferably at room temperature, for sufficient time for the reaction to proceed for example 3 hours to 24 hours;

or when R^6, R^7 or R^8 is a benzyloxy group, by deprotecting in the presence of palladium and sodium acetate in an acetic acid solvent at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at the temperature of boiling under reflux, for sufficient

time for the reaction to proceed, for example 1 hour to 12 hours. The compound represented by formula (XXIII) can be obtained by reacting the reactive halogenated derivative R^{13}-X(XX) with the compound represented by formula (XXII) in which R^6 is a hydroxyl group in the presence or absence of KI, using an inorganic base such as for example potassium carbonate, cesium carbonate, calcium carbonate or the like or an organic base such as for example triethylamine, pyridine, N,N-dialkylaniline or the like, but preferably potassium carbonate, and using as solvent, a polar solvent such as for example acetonitrile, dimethylformamide (DMF), dimethylsulfoxide (DMSO) or the like, or an ether type solvent such as for example THF, dioxane, DME or the like, but preferably DMSO, at from room temperature to 80°C, but preferably at room temperature, for sufficient time for the reaction to proceed, for example 1 hour to 12 hours. When R^7 is a hydroxyl group, a reaction can be caused with acetyl chloride and bromoacetic acid ester and when R^8 is a hydroxyl group, a reaction can be caused with acetyl chloride.

Moreover, for compounds represented by general formula (XXIV) wherein the compound represented by general formula (XXII) has suitable substituents converted when R^6 is a 1-6C straight chain alkyl group optionally substituted by a 4-methoxyphenoxy group, for example, when R^6 is a 2-(4-methoxyphenoxy) ethyloxy group, 3-(4-methoxyphenoxy) propyloxy group, 4-(4-methoxyphenoxy) butyloxy group or the like, it can be derived into a compound represented by general formula (I), for example a compound wherein R^1 is a 2-hydroxyethyloxy group, 3-hydroxypropyloxy group, 4-hydroxybutyloxy group or the like by deprotecting in the presence of cerium ammonium nitrate (CAN) in a mixed solvent of acetonitrile and water or in acetonitrile, but preferably in a mixed solvent of acetonitrile and water, at from under ice cooling to the temperature at which the reaction mixture boils under reflux, but preferably at 0°C, for sufficient time for the reaction to proceed, for example 15 minutes to 4 hours.

As far as other substituent conversions are concerned, when R^6 or R^7 is a halogen atom, a conversion to an amino group can be carried out by reacting in the presence of copper and copper iodide, in an aqueous ammonia solution at a temperature of 150-200°C, but preferably at the temperature of 180-190°C, for sufficient time for the reaction to proceed, for example 3 hours to 12 hours; or a conversion to a cyano group can be carried out by reacting in the presence of copper cyanide in DMF at a temperature of 100-200°C, preferably at temperature of 120-140°C, for sufficient time for the reaction to proceed, for example 1 hour to 12 hours.

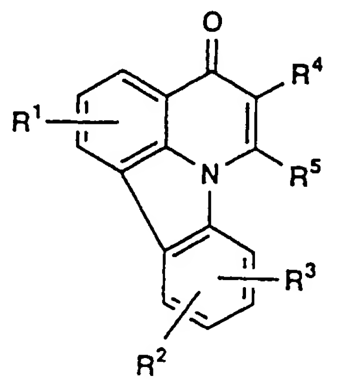
Moreover, if R^6 or R^7 is a nitro group, the conversion to an amino group can be carried out by reacting in the presence of copper, using dilute sulfuric acid as solvent at room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at 50°C, for sufficient time for the reaction to proceed, for example, for 30 minutes to 3 hours.

When R^6 or R^7 is amino group, a conversion to a hydroxyl group can be carried out by reacting in the presence of sodium nitrite, using dilute sulfuric acid as solvent, at from under ice-cooling to the temperature at which the reaction mixture boils under reflux, but preferably at the temperature of heating under reflux, for sufficient time for the reaction to proceed, for example 5 minutes to 3 hours.

When R^6 or R^7 is an acetyl group, halogenation may be carried out in the absence or co-presence of for example light, a peroxide such as benzoyl peroxide (BPO) or the like or AIBN, but preferably in the absence thereof, using a suitable halogenating agent such as for example chlorine gas, bromine, cuprous bromide, N-bromo succinimide (NBS), N-chlorosuccinimide (NCS), trihalogeno methane sulfonyl halide, trichloro bromomethane, phenyl trimethylammonium tri bromide (PTT) or the like, but preferably PTT, and using as solvent, a halogenated hydrocarbon solvent such as for example carbon tetrachloride, chloroform, methylene chloride or the like, an aromatic hydrocarbon system non-polar solvent such as for example benzene, toluene or the like, an ether type solvent such as for example THF, dioxane, DME or the like, or an acetic acid or carbon disulfide solvent, but preferably THF, from at room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at the temperature of boiling under reflux, for sufficient time for the reaction to proceed, for example 1 hour to 12 hours, and thereafter reaction with aniline, N-methylaniline, morpholine or the like can be carried out using an inorganic base such as for example potassium carbonate, cesium carbonate, calcium carbonate, sodium bicarbonate or the like or an organic base such as for example triethylamine, pyridine, N,N-dialkylaniline or the like, but preferably sodium bicarbonate, and using as solvent, a polar solvent such as for example acetonitrile, dimethylformamide (DMF) or the like, a halogenated hydrocarbon solvent as exemplified by chloroform or methylene chloride, an ether type solvent as exemplified by ether or THF, or an alcohol system solvent such as for example methanol, ethanol or the like, but preferably ethanol, at from room temperature to the temperature at which the reaction mixture boils under reflux, preferably at the temperature of boiling under reflux, for sufficient time for the reaction to proceed, for example 1 hour to 12 hours.

When R^6 or R^7 is halogen atom, dehalogenation can be carried out in the presence of palladium using acetic acid as solvent at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at the temperature of boiling under reflux, for sufficient time for the reaction to proceed, for example 1 hour to 12 hours. These substituent conversions can be carried out also for R^8.

The compounds of formula (I)



(I)

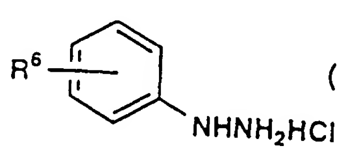
or salts thereof can be produced by further carrying out substituent conversion in accordance with requirements.

The compounds represented by formula (I) or salts thereof can be also produced by reacting the compound represented by formula (XXIV) obtained by substituent conversion of R^6, R^7 and R^8 in the compound of formula (XXII) by the same aforesaid reaction with a reactive halogenated derivative represented by formula (XX) in the same way as described above.

<u>Process for Production 2</u>

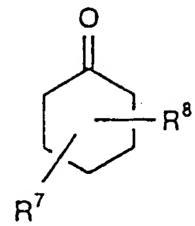
The compound of formula (I) is synthesized efficiently in some cases by Process for Production 2 or Process for Production 3 depending on the position and species of substituent, the number of substituents and the selectivity of the ring closure.

Phenylhydrazines represented by following formula (V)



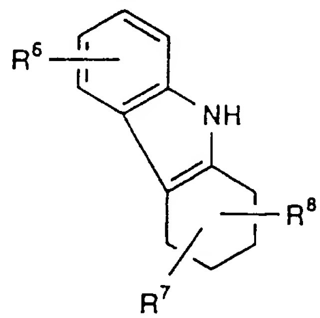
(V)

and cyclohexanones represented by following formula (XIV)



(XIV)

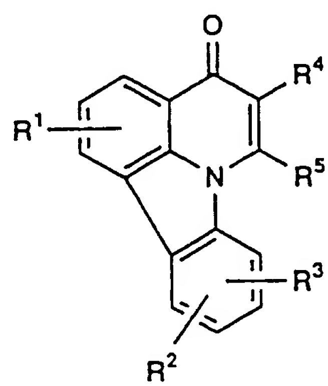
or salts thereof can be derived into tetrahydrocarbazole derivatives represented by formula (VI)



(VI)

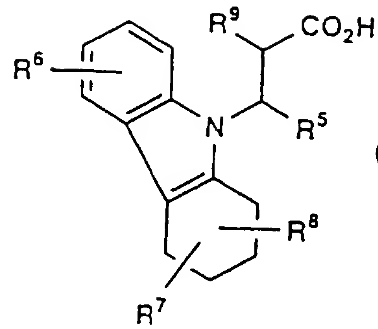
by carrying out a Fischer's indole synthesis in the presence of zinc chloride, Lewis acid and proton acid catalyst, but preferably in the absence of catalyst, using acetic acid as solvent at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at the temperature of boiling under reflux for sufficient time for the reaction to proceed, for example 1 hour to 3 hours.

Thereinafter, the compound represented by following formula (I)



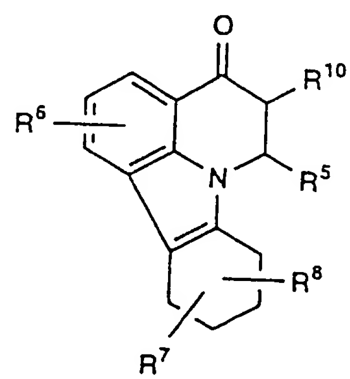
(I)

or a salt thereof can be produced by carrying out derivitisation to following formula (VII)



(VII)

by the same process as in the production method for from formula (II) to formula (III) in Process for Production 1, and thereafter carrying out a cyclization reaction by the same process as in the production method for from formula (III) to formula (IV) in Process for Production 1 via following formula (VIII),

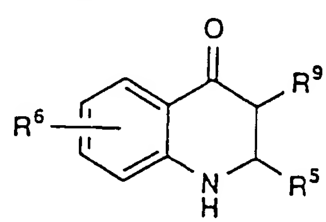


(VIII)

and in addition to the same process as in the production method from formula (IV) to formula (I) in Process for Production 1, via an aromatic cyclization using DDQ.

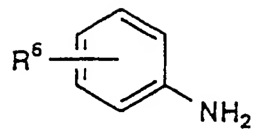
<u>Process for Production 3</u>

The compound of following formula (XI)



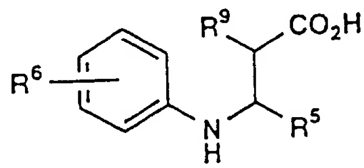
(XI)

can be obtained by a cyclization reaction of an aniline derivative represented by following formula (IX)



(IX)

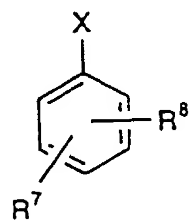
or a salt thereof by the same process as in the production method from formula (III) to formula (IV) in Process for Production 1, via following formula (X)



(X)

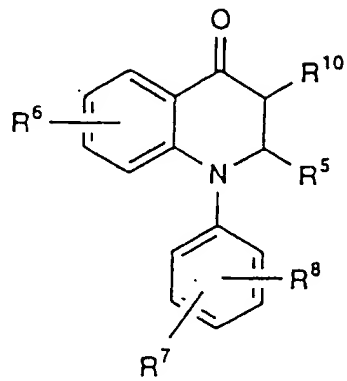
by the same process as in the production method from formula (II) to formula (III) in Process for Production 1.

The desired substituted phenyl group is introduced by carrying out an Ullmann reaction of this compound and aryl halide represented by following formula (XV)



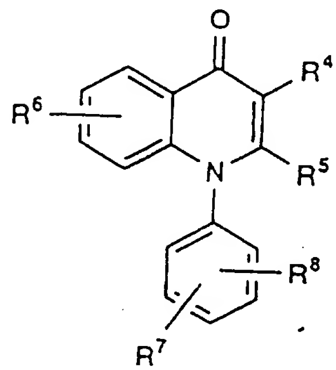
(XV)

in the presence of copper powder, copper oxide or iron powder, but preferably in the presence of copper oxide, using an inorganic base such as for example potassium hydroxide, potassium carbonate or the like, an alkali metal reagent such as for example sodium alkoxide, sodium hydroxide or the like, but preferably potassium carbonate in the absence of solvent or in a suitable high boiling point solvent such as DMF, DMSO, DME, dibutyl ether, xylene, decalin, 1,3-dimethyl-2-imidazolidone (DMI) or the like, but preferably in the absence of solvent, at 100-200°C, preferably 180-190°C for sufficient time for the reaction to proceed, for example 1 hour to 12 hours, and thereby a compound of (XII)



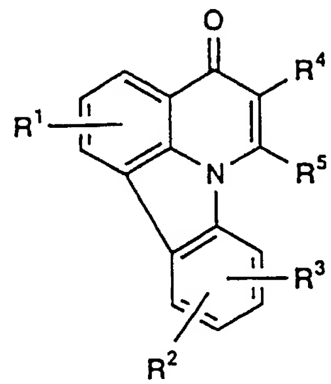
(XII)

is derived, and the compound of formula (XIII)



(XIII)

is obtained by the same production method from formula (IV) to formula (I) in Process for Production 1, and thereafter an aromatic carbon-carbon bond formation reaction is carried out in the presence of palladium acetate, boron trifluoride acetic acid complex, palladium chloride or the like, but preferably in the presence of palladium acetate, using as solvent for example acetic acid, trifluoroacetic acid, methanesulfonic acid or the like, but preferably acetic acid, at from room temperature to the temperature at which the reaction mixture boils under reflux, but preferably at the temperature of boiling under reflux for sufficient time for the reaction to proceed, for example 1 hour to 5 hours, and in accordance with requirements, the same substituent conversion reaction as in Process for Production 1 is carried out, and thereby the compound of (I)



(I)

or a salt thereof is obtained.

Moreover, when a reactive group such as for example a hydroxyl group, amino group, carboxyl group, thiol group or the like are present as substituents in any compound synthesized by the aforesaid process for production, these groups are suitably protected in each reaction step and the aforesaid protecting group eliminated at a suitable stage. Such introduction and elimination of protecting groups are suitably carried out according to the type of the group to be protected or the protecting group, and these can be carried out in accordance with Protective Groups in Organic Synthesis, Second Edition, 1991.

Moreover, compounds at any process for production step, may be subjected to oxidation or cyclization of functional groups using conventional procedures in accordance with requirements.

The terms in the specification of this invention will now be described.

By pulmonary hypertension there are meant various diseases presenting pulmonary hypertension, namely, chronic bronchitis, peripheral respiratory tract lesion, pulmonary emphysema, bronchiectasis, sarcoidosis, tuberculosis after-effects, diffuse interstitial pneumonia, diffuse bronchiolitis, asthma, pulmonary fibrosis, collagen disease, pulmonary thromboembolism, pulmonary veno-occlusion, lung vasculitis, primary pulmonary hypertension and the like, and furthermore, diseases such as pulmonary heart in which pulmonary hypertension has progressed are also included.

Patients presenting pulmonary hypertension have a disturbance in the pulmonary circulation due to pulmonary vascular occlusion, and cyanosis and dyspnea are caused. Palpitation, pectoralgia are often seen and coughing is also frequent.

By ischemic heart disease herein, there is meant a general term for diseases generated as a result of circulatory disorders in the heart due to various causes, and examples include effort angina, rest angina, unstable angina, variant angina, acute cardiac insufficiency, chronic cardiac failure, cardiac infarction, cardiac edema, arrhythmia and the like.

Patients having ischemic cardiac disease have anginal pain such as chest pain, a feeling of chest tightness or the like which occurs transiently or continuously and is accompanied by feebleness, vertigo, breathlessness, vomition or consciousness disorder. In cardiac failure, dyspnea and cyanosis are observed, and because of a marked fall in blood pressure, shock symptoms such as for example bradycardia, cold sweat, paleness or the like are also observed.

By diseases for which cGMP-PDE inhibitory action is effective, there is meant a general term for diseases wherein an increase in cGMP is seen as effective. In addition to the above, other examples include arterial sclerosis, restenosis after PTCA or the like, thrombosis (thrombosis occurring due to injuries to blood vessel walls, arteriosclerosis, vasculitis, platelet aggregation or the like), asthma, chronic obstructive lung diseases (bronchitis, lung emphysema), glomerular diseases including glomerulonephritis and diabetic nephropathy, renal failure, nephritis edema, diseases of the urinary organs and reproductive organs (for example prostate gland hypertrophy, erectile dysfunction and incontinence), peripheral circulation disorder, peripheral vascular disease, cerebral circulation disorder (cerebral infarction or the like), cerebral function disorder, dementia, allergic disease (atopic dermatitis, allergic rhinitis), hypertension and the like.

Renal failure comprises a pathological state or clinical various symptoms due to a lowering of renal function due to various causes, namely a lowered quantity of glomerular filtration (GFR). Moreover, some of the glomerular bodies show a sclerotic image in chronic renal failure, and renal failure is thought to progress together with the spread of sclerosis to glomerular bodies having less disorder. As a result, there is an escalation in the accumulation of various excretion substances in the body, and so-called uremia occurs. Moreover, polyuria, night urination is also observed due to a disorder in the condensing effect. In renal failure, if there is inappropriate Na or water stress, adequate compensation is not possible because of the lowered GFR, and edema, lung edema, congestive heart failure, hypertension and the like are observed.

Test Examples

The pharmacological action, toxicity and the like of representative compounds of this invention will now be illustrated in greater detail using Examples, but it should be understood however that this invention is not restricted in any way to these Examples.

Test Example 1

(PDE inhibitory action).

Experimental method

Based on the experimental process of Lugnier et al. in BioChem. Pharmacol. Vol 35, pp. 1743-1751, 1986, PDE from dog aorta was purified. The dog aorta was cut into small pieces under ice cooling in a 6 fold volume of 20 mM tris HCl buffer of pH 7.5 which contained 2 mM magnesium acetate, 5 mM ethylene diamine tetraacetic acid (EDTA), 100 μg/ml of phenylmethyl sulforyl fluoride, and 15 mM 2-mercaptoethanol (2-ME), and this was homogenized using a Waring blender and glass homogenizer, and centrifuged at 1200 x g for 30 minutes. The centrifugal supernatant was collected, and ammonium sulfate was added so as to form 45 % saturation, and salting out was carried out. The obtained precipitate fraction was resuspended in 20 mM Tris-hydrochloric acid buffer of pH 7.5 containing 2 mM magnesium acetate and 1 mM 2-ME, and this was dialyzed overnight and then loaded onto a DEAE-Tris acryl column (DEAE TRISACRYL M: IBF). Elution was carried out with a sodium chloride gradient of 0-0.4 M, and PDE type V and PDE type III were separated from the other isozymes. On the other hand, further ammonium sulfate was added to the 45 % saturated ammonium sulfate supernatant liquid fraction so as to form 65 % saturation, and the fraction obtained by precipitation was loaded in the same way on to a DEAE-Tris acryl column, and this was eluted with a sodium chloride gradient of 0-0.4 M, and PDE type 1 was separated.

Using the obtained PDE type V, type III and type I, the activity was measured in accordance with the method of Thompson et al. (Adv. Cyclic Nucleotide Res. Vol 10, pp. 69-72, 1979) and Wells et al. (Biochem. Biophys. Acta, Vol 384, pp. 430-443, 1975). In other words, PDE was added to 50 mM Tris-hydrochloric acid buffer of pH 7.5 containing 1 μM substrate, cGMP or cAMP (containing tritium labelled cGMP or cAMP), 1 mM EGTA and 2 mM magnesium acetate. The PDE activity was determined by a method wherein the enzymically formed 5'-GMP or 5'AMP was further decomposed to guanosine or adenosine with snake venom, separated from the substrate using ionic exchange resin (Dowex 1-X2), and measurement was carried out with a scintillation counter. The activity of the test compound was calculated as the rate of inhibition from the PDE activity measured when each test

compound was added as a dimethylsulfoxide (DMSO) solution to this reaction system, and the IC_{50} value (50 % inhibition concentration) was calculated using the Probit method. The final DMSO concentration was made 2 % or less on consideration of the effect on PDE activity. The results are shown in Table 1.

Table 1.
PDE inhibiting activity

Example number	Inhibiting activity IC50 (μM)		
	Type V	Type III	Type I
2	0.10	3.6	>30
3	0.0075	>30	>30
4	0.0038	6.8	>30
5	0.0055	19	>30
7	0.0043	>30	>30
15	0.045	15	>30
18	0.059	1.9	>30
22	0.11	11	>30
48	0.10	>100	>100
49	0.10	198	>300
50	0.0015	>30	>30
51	0.0017	>30	>30
52	0.0035	>30	>30
57	0.015	>30	>30
58	0.050	>10	>10
59	0.030	>100	>100
60	0.0009	15	>30
61	0.0008	>30	>30
62	0.0020	>30	>30
63	0.19	>30	>30
64	0.011	81	>100
66	0.010	>30	>30

Table 1 (continued).

PDE inhibiting activity

Example number	Inhibiting activity IC50 (μM)		
	Type V	Type III	Type I.
76	0.021	>30	>30
82	0.10	>100	>100
83	0.0047	>30	>30
101	0.0047	>30	>30
102	0.0073	9.3	>30
103	0.091	>30	>30
104	0.0032	3.5	>30
105	0.018	2.4	>30
106	0.088	>30	>30
107	0.021	>30	>30
109	0.067	14	>30
110	0.0079	10	>30
121	0.026	>30	>30
122	0.0090	13	>30
155	0.36	7.3	48
156	0.20	5.6	>30
193	0.43	6.9	>100
226	0.060	12	>30
245	0.042	3.9	>30
264	0.080	>30	>30
277	0.040	>30	>30
283	0.014	3.6	>30
289	0.017	2.5	>30

A remarkable PDE type V inhibitory action and high enzyme inhibition selectivity were observed for all of the compounds of this invention.

Test Example 2

(Pulmonary artery pressure reducing action).

Experimental Method.

Hybrid adult dog was anaesthetized by administering ketamine 20 mg/kg intramuscularly and 5 mg/ml α-chloralose - physiological saline 20 ml/kg intravenously, and under artificial respiration, the aorta pressure was measured by inserting a catheter from the femoral artery, and the pulmonary artery pressure was measured by inserting a Swan-Ganz catheter into the pulmonary artery from the jugular vein. Anaesthesia was maintained by intravenous administration of 5 mg/ml α-chloralose - physiological saline at 5 ml/kg/hour, and nitroglycerin, nifedipine or test compound 0.01-1 mg/kg was administered intravenously, and a comparison was made. The administration was carried out by injecting a volume of 0.3 ml/kg from the right femural vein, and the test compound was dissolved in dimethylformamide (DMF) and diluted by adding polyethylene glycol 200 and water sequentially, so as to have ratios of 20, 50, 30 % (v/v %) respectively. The results are shown in Table 2, wherein the maximum value for the percentage pulmonary artery pressure loss and maximum value for the percentage aorta pressure loss are taken as the pulmonary arterial pressure depressing action and systemic blood pressure depressing action respectively.

Table 2

Pulmonary artery pressure depressing action

Example number	Dose (mg/ kg)	Pulmonary arterial pressure loss (%)	Systemic blood pressure loss (%)
3	0.3	19	12
50	0.3	33	13
60	0.3	20	8
102	0.3	24	19
105	0.1	16	12
109	0.3	19	11
110	0.3	23	7
193	0.3	16	1
279	0.3	17	4
285	0.3	16	2
291	0.3	13	4
Nitroglycerin	0.01	19	30
Nifedipine	0.01	3	18

The compounds of this invention demonstrate a high pulmonary artery blood pressure reduction rate compared with the systemic blood pressure reduction rate, and have selectivity for the pulmonary

artery pressure. In contrast to this, the nitroglycerin and the nifedipine used as reference agents lowered the systemic blood pressure by a larger percentage than the pulmonary artery pressure.

Test Example 3.

(Coronary artery diameter increasing action).

Experimental Method.

The thorax of a hybrid adult dog was opened under α-chloralose anesthesia, and the left coronary artery branch was separated and the coronary artery diameter was measured by attaching a pair of ultrasonic crystals to the adventitial cells, and the coronary artery blood flow was measured by attaching an electromagnetic blood flow meter probe to the peripheral side thereof. Nitroglycerin, dipyridamole or the test compound was administered intravenously, and a comparison was carried out. Test compounds were dissolved in dimethylformamide, and diluted by adding polyethylene glycol 200 and water in this order, and the solutions prepared so that the proportions thereof were 20, 50 and 30 % (v/v%). The results are shown as the respective ratio of the maximum values of the changed ratio of the coronary artery diameter and coronary artery blood flow with respect to the changed ratio when nitroglycerin 10 μg/kg was used. The results are shown in Table 3.

Table 3

Coronary artery diameter increasing action.

Example number	Dose (mg/kg).	Ratio with respect to nitroglycerin Coronary artery diameter	Coronary artery blood flow
155	1	1.47	0.79
193	1	1.44	1.40
278	1	1.50	0.04
Dipyridamole	0.03	0.17	2.66

The dipyridamole used as the control agent showed a much greater coronary artery blood flow rate increasing action indicating a narrow blood vessel dilation compared to coronary artery diameter increasing action. However, the compounds of this invention increased the coronary artery diameter more than the coronary artery blood flow rate, and caused selective relaxation of the thicker part of coronary artery to at least the same extent as nitroglycerin, and did not have an action akin to that of dipyridamole namely affording an increase in coronary artery blood flow more than the coronary artery diameter.

Test Example 4

(Toxicity experiment).

The toxicity of compounds of this invention was examined. The compounds of Examples of this invention numbers 3, 50, 102, 105, 109, 110 and 193 were administered orally to 4-week-old Wistar male rats at 100 mg/kg/day for four days, and observations were carried out. As a result, there were no cases of death up to the day after the completion of the administration, and no abnormalities were observed in body weight or general symptoms.

In accordance with the aforesaid Test Examples, the compounds of this invention were shown to have a marked PDE type V inhibitory action and extremely high enzyme inhibition selectivity. Moreover, the compounds of this invention in the living body showed relatively higher pulmonary artery pressure lowering ratio compared to systemic blood pressure lowering ratio and so had selectivity with respect to the pulmonary artery pressure; the compounds increased the coronary artery diameter much more than the coronary artery blood flow rate, and were shown to selectively relax the thick parts of the coronary artery to at least the same extent as nitroglycerin, which is the most reliable angina pectoris therapeutic drug. Accordingly it was suggested that there was no direct action on the heart, and the steal phenomenon and resistance would not be produced. In addition to this, the compounds of this invention were shown to inhibit blood platelet aggregation. Moreover, it was shown that the toxicity of compounds of this invention was low as no kinds of abnormality were observed in the toxicity test.

Accordingly the compounds with the pyridocarbazole skeleton of this invention have a marked PDE type V inhibitory action and extremely high enzyme inhibition selectivity, and also showed effectiveness in animal models, and therefore they are effective in the prevention or therapy of pulmonary hypertension and ischemic heart disease. Moreover, the said compounds are useful as circulation regulator during surgical operations and also after operations.

As pulmonary hypertension disorder, various diseases presenting pulmonary hypertension may be nominated, namely examples include chronic bronchitis, peripheral respiratory tract lesion, emphysema, bronchiectasis, sarcoidosis, tuberculosis after-effects, diffuse interstitial pneumonia, diffuse bronchiolitis, asthma, pulmonary fibrosis, collagen disease, pulmonary thromboembolism, pulmonary venous occlusion, pulmonary vasculitis and primary pulmonary hypertension and the like, and also diseases such as pulmonary heart in which pulmonary hypertension has progressed.

Patients presenting pulmonary hypertension have a disturbance in pulmonary circulation due to pulmonary vascular occlusion, and cyanosis, dyspnea are caused. Moreover, palpitation and pectoralgia are often observed and coughing is also frequent.

By ischemic heart disease in this case there is meant a general term for diseases generated as a result of circulatory disorders in the heart due to various causes, and examples include effort angina, rest angina, unstable angina, variant angina, acute cardiac insufficiency, chronic cardiac failure, cardiac infarction, cardiac edema, arrhythmia and the like.

Patients having ischemic cardiac disease have anginal pain such as chest pains, feelings of chest tightness and the like that occurs transiently or continuously, which is accompanied by feebleness, vertigo, breathlessness, vomition and consciousness disorder. In cardiac failure, dyspnea and cyanosis are observed, and because of the marked fall in blood pressure, shock symptoms such as for example bradycardia, cold sweat, paleness and the like are also observed. Medicinal compositions of this invention are effective for various symptoms such as above.

The compounds of this invention because they markedly increase cGMP, can be used in arteriosclerosis, restenosis after PTCA and thrombosis (thrombosis occurring due to trauma of blood vessel walls, arteriosclerosis, vasculitis, platelet aggregation or the like). More particularly, these coronary artery diseases are attracting attention as a factor in ischemic heart disease, and therefore these compounds are expected to form a more highly effective ischemic heart disease prophylactic and/or therapeutic drug.

The proliferation of the vascular smooth muscle cells which is one of the causes of these arteriosclerotic diseases in the coronary arteries is thought be heavily linked with post-PTCA coronary artery restenosis or arteriosclerotic blood vessel hyperplasia at other sites and the like, and these diseases can be prevented by increasing cGMP, leading to the inhibition of the proliferation of vascular smooth muscle cells in arteriosclerosis and restenosis after PTCA. Moreover, among diseases presenting pulmonary hypertension, for example in the early pathogenic stages of pulmonary edema and bronchitis, there is no accompanying pulmonary hypertension, but with prolonged insufficient ventilation, a disturbance in the pulmonary circulation appears due to pulmonary blood vessel hyperplasia or very small artery smooth muscle hyperplasia or the like, and this is thought to gradually progress to irreversible pulmonary hypertension, and therefore, if preventive

administration is carried out on consideration of suppression of vascular smooth muscle cells in the early stages, the suppression of a pathogenesis of subsequent pulmonary hypertension is thought possible.

Moreover, as diseases in which a cGMP-PDE inhibitory action is effective, in addition to the aforesaid diseases, the said compounds can be used for asthma, chronic obstructive pulmonary disease (bronchitis, pulmonary edema), glomerular disease such as glomerulonephritis, diabetic nephropathy, renal failure, nephritis edema, genitourinary disease (for example prostate gland hypertrophy, erectile dysfunction and incontinence), peripheral circulation, peripheral vascular disease, cerebral circulation disorder (cerebral infarction or the like), cerebral function disorder, dementia, allergic disease (atopic dermatitis, allergic rhinitis), hypertension and the like, wherein increased cGMP would be considered effective. In particular, the said compounds can be used for asthma, chronic obstructive lung disease (bronchitis, pulmonary edema), glomerular disease including glomerulonephritis, diabetic nephropathy, renal failure, nephritis edema, genitourinary disease (for example prostate gland hypertrophy, erectile dysfunction and incontinence).

Renal failure is a pathological state or clinical various symptoms due to a drop in renal function based on various causes, namely a fall in the quantity of glomerular filtration (GFR). Moreover, some of the glomerular bodies show a sclerotic image in chronic renal failure, and the renal failure is thought to progress together with the spread of sclerosis to glomerular bodies having less disorder. The fall in the glomerular function differs in accordance with the various causes of the disease, but an improvement in kidney hemodynamics as a result of increased cGMP leads to a rise in GFR, and as a result, the in-vivo accumulation of various excretion substance is inhibited, and an improvement in uremia is possible. Moreover, it is also possible to improve polyuria, night-time urination, caused by concentration ability disorder. In renal failure, when unsuitable Na or water load is present, an adequate compensation is not possible because of the decreased GFR, and edema, pulmonary edema, congestive cardiac failure, hypertension and the like are observed, but these can be improved. Moreover, because cGMP increase can suppress proliferation of mesangial cells and substrate, the said compounds can suppress glomerular sclerosis, and suppress the progression of glomerular disease and renal failure. In other words, by increasing cGMP, the progression from kidney failure to terminal stage kidney, which had been considered to be difficult to halt with the prior art drugs, can be suppressed and kidney dialysis may be avoided.

The drugs of this invention are administered in the form of a medicinal composition.

The medicinal compositions of this invention may contain one or more of the compounds represented by formula (I) of this invention, and are produced in combination with a pharmaceutically acceptable carrier. More particularly, various formulations can be produced by combining the compound of this invention with an excipient (for example, lactose, refined sugar, mannitol, crystalline cellulose or silica), binding agent (for example, crystalline cellulose, saccharide (mannitol or refined sugar), dextrin, hydroxypropylcellulose (HPC), hydroxymethyl cellulose (HPMC), polyvinylpyrrolidone (PVP), macrogol), lubricant (for example; magnesium stearate, calcium stearate or talc), colorant, flavouring agent, disintegrating agent (for example; maize starch or carboxymethylcellulose), preservatives, isotonizing agent, stabilising agent (for example, sugar or sugar alcohol), dispersant, antioxidant (for example, ascorbic acid, butyl hydroxyanisole (BHA), propyl gallate or dl-α-tocopherol), buffer agent, preservative (for example, paraben, benzyl alcohol or benzalkonium chloride), aroma agent (for example, vanillin, 1-menthol or rose oil), solubilizer (for example, cholesterol or triethanolamine), suspending agent or emulsifier, generally used suitable carrier or solvent.

Tablets, capsule formulations, granules, powders, suppositories, vaginal suppositories, syrups (peroral liquid agents, emulsifiers), inhalants, topical agents, injections and the like may be proposed as such formulations, and as such can be administered to the patient orally or parenterally (for example by intravenous administration, intraarterial administration, subcutaneous administration, intramuscular administration, rectal administration, vaginal administration, percutaneous absorption or per mucosal absorption or the like).

The dose of this invention is usually 0.1 mg - 2.5 g, preferably 0.5 mg - 1.0 g, and more preferably 1 mg - 500 mg per day for an adult. However, it can be increased or decreased as appropriate in accordance with the symptoms or administration route.

The whole quantity can be administered orally or parenterally in a single dose, or divided into 2-6 doses, and it can also be administered continuously, for example by a drip infusion.

Examples

This invention will now be described in greater detail by reference to Examples, but it should be understood however that this invention is not limited to these Examples.

Each measurement was carried out using the following equipment, namely a JEOL JNM-EX270 FT-NMR (made by JEOL company) or JEOL JNM-LA300 FT-NMR (made by JEOL Co., indicated by * in the data) for the NMR, a HORIBA FT-200 (made by Horiba, Ltd.) for the IR, and a Mettler FP-80, FP-82, FP-81HT or FP-90 (all made by Mettler Co. Ltd.) for the melting point were respectively used. In the Examples, the yield quantity and yield are shown within the brackets subsequent to "the title compound".

Example 1

Synthesis of 10-bromo-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one.

Step 1

Synthesis of 3-bromo-6-methoxy carbazole

At room temperature, to anhydrous methanol (260 ml) was added and dissolved therein 23.3 g of sodium a little at a time. Thereafter, anhydrous dimethylformamide (1400 ml), steel iodide (117 g) and 3,6-dibromocarbazole (100 g) were added successively and the mixture was heated under reflux under an argon atmosphere for two hours. The reaction liquor was filtered using celite while heating, allowed to cool, and thereafter water (2 l) was added and extraction was carried out with methylene chloride. The methylene chloride layer was washed successively with water, 1N hydrochloric acid, water and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel column chromatography (eluting solvent: hexane : methylene chloride = 1 : 1), and the title compound (33.4 g, 39 %) was obtained.

mp.: 149.9-151.1°C.

IR spectrum (KBr tablet) ν cm^{-1} : 3390, 2900, 1491, 1205, 1169, 806

NMR spectrum (DMSO-d_6) δ ppm:11.23 (1H, s), 8.36 (1H, s), 7.78 (1H, d, J = 2.0 Hz), 7.48-7.40 (3H, m), 7.07 (1H, dd, J = 8.8, 1.5 Hz), 3.84 (3H, s).

Step 2

Synthesis of 3-bromo-6-methoxy carbazole-N-β-propionic acid

The compound obtained in Step 1 (30 g) was suspended in 80 ml acetone and cooled to 0°C on an ice bath, methyl acrylate (25 ml) was added, and thereafter Triton B (10 ml) was added dropwise. The ice bath was removed and the mixture was stirred at room temperature for 1 hour, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue thereby obtained was

suspended in 30 ml methanol, and sodium hydroxide (10 g) dissolved in water (60 ml) was added dropwise at room temperature and the mixture refluxed for 20 minutes. The solvent was eliminated under reduced pressure, and thereafter water and ether were added and liquid separation was caused. The aqueous layer was made acidic by the addition of 4 N hydrochloric, and thereafter the thereby formed precipitate was dissolved in ethyl acetate, washed with water and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The crude crystals of the residue were washed with hexane-ether and recovered by filtration, and the title compound (33.6 g, 88 %) was obtained.

mp.: 149.7-152.1°C

IR spectrum (KBr tablet) ν cm^{-1}: 3425, 2920, 1705, 1697, 1491, 1298, 802

NMR spectrum (DMSO-d_6) δ ppm: 8.38 (1H, d, J = 1.5 Hz), 7.81 (1H, d, J = 2.4 Hz), 7.59-7.49 (3H, m), 7.11 (1H, dd, J = 8.8, 2.4 Hz), 4.57 (2H, t, J = 6.8 Hz), 3.84 (3H, s), 2.67 (2H, t, J = 6.8 Hz).

Step 3

Synthesis of 10-bromo-5,6-dihydro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 2 (24 g) was suspended in anhydrous chloroform (500 ml) and thereto was added PPE (118 g) dissolved in anhydrous chloroform (350 ml) at room temperature, and the mixture was heated under reflux under an argon atmosphere for 1 hour. After allowing to cool, the mixture was discharged into 1N sodium hydroxide (500 ml) and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: hexane : methylene chloride = 1 : 3), and thereafter the title compound (17.1 g, 75 %) was obtained by washing the crude purified material with methanol and recovering by filtration.

mp.: 175.2-176.1°C.

IR spectrum (KBr tablet) ν cm^{-1}: 2910, 1672, 1497, 1479, 797

NMR spectrum (DMSO-d_6) δ ppm: 8.49 (1H, s), 8.14 (1H, d, J = 2.4 Hz), 7.64 (2H, bs), 7.36 (1H, d, J = 2.0 Hz), 4.54 (2H, t, J = 7.1 Hz), 3.88 (3H, s), 3.13 (2H, t, J = 7.1 Hz).

Step 4

Synthesis of 10-bromo-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

To an ethanol (600 ml) suspension of the compound obtained in Step 3 (27 g) was added at room temperature pyridine-3-aldehyde (15 ml) and sodium hydroxide (20 g) dissolved in water (100 ml),

and the mixture was stirred at room temperature for 12 hours. The solvent was eliminated to about half the quantity by distillation under reduced pressure, and thereafter the precipitated crystals were recovered by filtration, washed successively with water, ethanol and ether, and the title compound (30 g, 87 %) was obtained.

Example 2

Synthesis of 10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (10.2g) obtained in Example 1 was suspended in anhydrous methylene chloride (1000 ml) and thereto was added dropwise boron tribromide (25 g) at room temperature, and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (500 ml) and thereto was added saturated sodium carbonate aqueous solution until there was no more effervescence, and the precipitated crystals were recovered by filtration. The title compound (6.4 g, 65 %) was obtained by washing the obtained crude crystals with methylene chloride and methanol mixed solution.

Example 3

Synthesis of 10-bromo-2-t-butoxycarbonyl methyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3-2,1-jk] carbazol-4-one (4.4 g) obtained in Example 2 was suspended in 250 ml dimethylsulfoxide, and potassium carbonate (4.5 g) was added and the mixture stirred at room temperature for 30 minutes, and thereafter bromoacetic acid t-butyl ester (2.1 ml) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (300 ml) and the mixture extracted with methylene chloride. The methylene chloride layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (3.4 g, 63 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: 3 % methanol-containing methylene chloride).

Example 4

Synthesis of 10-bromo-2-i-propoxy carbonyl methyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (3.6 g) obtained in Example 2 was suspended in 200 ml dimethylsulfoxide, and potassium carbonate (2.5 g) was added and the mixture stirred at room temperature for 30 minutes, and thereafter bromoacetic acid

i-propyl ester (1.4 ml) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (300 ml) and extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: 3 % methanol-containing methylene chloride) and thereafter the crude purified material was washed with ether and a small amount of methanol, and recovered by filtration and the title compound (2.6 g, 59 %) thereby obtained.

Example 5

Synthesis of 10-bromo-2-ethoxycarbonylmethyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (13.9 g) obtained in Example 2 was suspended in 500 ml dimethylsulfoxide, and potassium carbonate (9.5 g) was added and the mixture stirred at room temperature for 30 minutes, and thereafter bromoacetic acid ethyl ester (4.2 ml) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (500 ml) and the precipitated crystals were recovered by filtration. The crude crystals were refined by silica gel flash column chromatography (eluting solvent: 3 % methanol-containing methylene chloride), and thereafter the title compound (9.0 g, 53 %) was obtained by again precipitating the crude purified material using chloroform-hexane and recovering by filtration.

Example 6

Synthesis of 10-bromo-2-carboxymethyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-ethoxycarbonylmethyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (2 g) obtained in Example 5 was suspended in 100 ml ethanol, and 1N sodium hydroxide aqueous solution (20 ml) was added and the mixture stirred at room temperature for 12 hours. The solvent was eliminated by distillation under reduced pressure, and thereafter the residue was caused to undergo liquid separation between 4N sodium hydroxide and methylene chloride. The aqueous layer was adjusted to pH 6 by the addition of 4 N hydrochloric acid, and thereafter the title compound (1.8 g, 96 %) was obtained by recovering by filtration the thereby formed precipitated crystals.

Example 7

Synthesis of 10-bromo-2-n-propoxy carbonyl methyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Example 3, the title compound (170 mg, 55 %) was obtained from 10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) and bromoacetic acid n-propyl ester (0.1 ml).

Example 8

Synthesis of 10-bromo-2-(1-ethoxycarbonyl-1-methylethyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Example 3, the title compound (470 mg, 74 %) was obtained from 10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (500 mg) and α-bromo isobutyric ethyl ester (0.22 ml).

Example 14

Synthesis of 10-bromo-2-n-pentyloxy carbonyl methyloxy-5-(3-pyridyl methyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-carboxymethyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (300 mg) obtained in Example 6 was suspended in anhydrous benzene (10 ml) and thionyl chloride (0.95 ml) was added at room temperature and the mixture heated under reflux under an argon atmosphere for 3 hours. The solvent was eliminated by distillation under reduced pressure after allowing to cool, and anhydrous benzene (5 ml) was added and the solvent was eliminated by distillation once again. The thereby obtained residue was dissolved in anhydrous methylene chloride (3 ml) and was added dropwise under ice cooling to a methylene chloride (30 ml) solution of 1-pentanol (0.065 ml) and triethylamine (0.18 ml) and the mixture was stirred for 20 minutes. Water was added to the reaction liquor and the liquid extracted with methylene chloride. The methylene chloride layer was washed successively (sic) with saturated aqueous sodium chloride solution and was dried with anhydrous sodium sulfate. The crude crystalline residue were washed with ether and the title compound (200 mg, 58 %) was obtained by recovering by filtration.

Example 17

Synthesis of 10-bromo-2-(3-carboxy-1-trans-propenyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (400 mg) obtained in Example 2 was suspended in 30 ml dimethylsulfoxide, and potassium carbonate (0.3 g) was added and the mixture stirred at room temperature for 30 minutes, and thereafter 4-bromo ethyl crotonate (0.15 ml) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (300 ml) and extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. Purification of the residue was carried out by silica gel flash column chromatography (eluting solvent: ethyl acetate). The thereby obtained crude crystals were suspended in 20 ml ethanol, and 1N sodium hydroxide aqueous solution (5 ml) was added and the mixture stirred at room temperature for 12 hours. The solvent was eliminated by distillation under reduced pressure, and thereafter extraction was carried out with water and ethyl acetate. The aqueous layer was adjusted to pH 7 by the addition of 1 N hydrochloric acid, and thereafter the title compound (50 mg, 10 %) was obtained by recovering by filtration the thereby formed precipitated crystals.

Example 18

Synthesis of 10-bromo-5-(3-pyridylmethyl)-2-(3-pyridylmethyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (3.9 g) obtained in Example 2 was suspended in 230 ml dimethylsulfoxide, and potassium carbonate (4.0 g) was added and the mixture stirred at room temperature for 30 minutes, and thereafter 3-picolyl chloride hydrochloride (1.9 g) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (500 ml) and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed with methanol, and the title compound (2.9 g, 61 %) was obtained by recovering by filtration.

Example 22

Synthesis of 2-benzyloxy-10-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (2.0 g) obtained in Example 2 was suspended in a mixed solvent of anhydrous dimethylformamide (64 ml) and

anhydrous tetrahydrofuran (120 ml) and sodium hydride (260 mg, 60 %) was added under ice cooling. Thereafter, benzyl bromide (400 mg) was added dropwise and the mixture was stirred at room temperature for 12 hours. A small amount of methanol was added to the reaction liquor and thereafter extraction was carried out with ethyl acetate. The ethyl acetate layer was washed successively with 1N sodium hydroxide aqueous solution and saturated aqueous sodium chloride solution and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel column chromatography (eluting solvent: 3 % methanol-containing methylene chloride) and the title compound (1.7g, 67 %) was obtained.

Example 24

Synthesis of 2-(5-acetoxymethyl-3-pyridylmethyloxy)-10-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one.

Step 1

Synthesis of pyridine-3,5- dicarboxylic acid dimethyl ester

Pyridine-3,5-dicarboxylic acid (8.3 g) was suspended in anhydrous methanol (60 ml) and thionyl chloride (11 ml) was added dropwise at room temperature and the mixture heated under reflux under an argon atmosphere for 1 hour 30 minutes. After allowing to cool, the solvent was eliminated by distillation under reduced pressure and extraction was carried out with water-ethyl acetate. The ethyl acetate layer was washed with saturated sodium bicarbonate and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure and the title compound (7.5 g, 78 %) was thereby obtained.

mp.: 83.5-84.5°C

IR spectrum (KBr tablet) ν cm^{-1}: 1734, 1603, 1315, 1269, 1240, 995, 746.

NMR spectrum (*DMSO-d_6) δ ppm: 9.30 (2H, s), 8.66 (1H, s), 3.93 (6H, s).

Step 2

Synthesis of pyridine-3,5-dimethanol mono acetate

The compound obtained in Step 1 (11.9 g) was dissolved in anhydrous ether (300 ml) and was adjusted to 0°C on an ice bath. Thereafter, lithium aluminium hydride (6 g) was added a little at a time and the mixture was warmed gradually and stirred at room temperature for 12 hours. The reaction liquor was cooled on an ice bath once again, and methanol (400 ml) was added and the

solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel column chromatography (eluting solvent: 3 % methanol-containing chloroform) and thereafter the crude purified material was crystallized with hexane • ether mixed solution, and obtained as crude crystals. The thereby obtained crystals (3.4 g) were suspended in 10 ml pyridine and acetyl chloride (1.8 ml) was added dropwise at room temperature. On completion of the dropwise addition, the solvent was eliminated by distillation under reduced pressure, the residue was refined by silica gel column chromatography (eluting solvent: 3 % methanol-containing chloroform) and thereafter the title compound (1 g, 23 %) was obtained by washing the crude purified material with methanol and recovering by filtration.

mp.: 152.2-130.9°C

IR spectrum (KBr tablet) ν cm^{-1}: 3305, 2740, 2700, 1747, 1566, 1230, 1072

NMR spectrum (*DMSO-d_6) δ ppm: 8.79 (1H, s), 8.74 (1H, s), 8.37 (1H, s), 5.25 (2H, s), 4.68 (2H, s), 2.11 (3H, s).

Step 3

Synthesis of 3-acetoxymethyl-5-chloromethyl pyridine

The compound obtained in Step 2 (500 mg) was suspended in anhydrous benzene (8 ml) and thionyl chloride (0.2 ml) was added dropwise at room temperature and the mixture stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure, and the title compound (540 mg, 83 %) was obtained.

IR spectrum (neat) ν cm^{-1}: 3396, 3367, 1716, 1633, 1562, 1385, 1227, 1057.

NMR spectrum (*DMSO-d_6) δ ppm: 8.76 (1H, d, J = 1.8 Hz), 8.70 (1H, d, J = 1.8 Hz), 8.16 (1H, s), 5.20 (2H, s), 4.90 (2H, s), 2.10 (3H, s).

Step 4

Synthesis of 2-(5-acetoxymethyl-3-pyridylmethyloxy)-10-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (480 mg, 86 %) was obtained in accordance with Example 18 from 10-bromo-2-hydroxy-5-(3-pyridyl methyl)-4H-pyrido [3,2,1-jk) carbazol-4-one (400 mg) and the compound obtained in Step 3 (280 mg).

Example 25

Synthesis of 10-bromo-2-(5-hydroxymethyl-3-pyridylmethyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one.

To a 10 ml methanol suspension of 2-(5-acetoxymethyl-3-pyridylmethyloxy)-10-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (200 mg) obtained in Example 24 was added sodium hydroxide aqueous solution (a solution comprising sodium hydroxide 85 mg dissolved in water 0.8 ml) and the mixture was stirred at room temperature for 1 hour. The precipitated crystals were washed successively with methanol and ether, and the title compound (180 mg, 97 %) was obtained by recovering by filtration.

Example 26

Synthesis of 10-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

To a 40 ml dimethylsulfoxide suspension of 10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (0.6 g) obtained in Example 2 was added potassium carbonate (0.8 g) and the mixture was stirred at room temperature for 30 minutes, and thereafter 3-bromo-1-propanol (0.3 ml) was added and the mixture was stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (500 ml) and extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution and then with anhydrous sodium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (0.25 g, 37 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: 3 % methanol-containing methylene chloride).

Example 32

Synthesis of 10-bromo-2-(4-hydroxy-2-oxobutyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one.

Step 1

Synthesis of 4-chloro acetoacetic acid ethyl ester ethylene acetal

4-chloro acetoacetic acid ethyl ester (5 g), ethylene glycol (17 ml) and tosyl acid (0.1 g) were added to benzene and the mixture heated under reflux under an argon atmosphere for 16 hours (during this procedure, water was forcibly eliminated from within the system using a Dean Stark reaction apparatus). The reaction liquor was allowed to cool and thereafter discharged into water and extracted

with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution and the solvent was eliminated by distillation under reduced pressure after washing (sic) with anhydrous sodium sulfate. The title compound (2.0 g, 32 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: hexane : ethyl acetate = 20 : 1).

IR spectrum (neat) ν cm^{-1} : 2983, 2900, 1736, 1207, 1101, 1032

NMR spectrum (*$CDCl_3$) δ ppm: 4.17 (2H, q, J = 7.0 Hz), 4.08 (4H, s), 3.75 (2H, s), 2.85 (2H, s), 1.28 (3H, t, J = 7.0 Hz).

Step 2

Synthesis of 4-chloro-1-butanol-3-one ethylene acetal

The compound obtained in Step 1 (1.41 g) was dissolved in anhydrous tetrahydrofuran (50 ml) and lithium aluminium hydride (0.26 g) was added a little at a time under ice cooling and the mixture was stirred for 1 hour. Under ice cooling, saturated ammonium chloride aqueous solution was added a little at a time until no effervescence was caused, and thereafter water was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution and the solvent was eliminated by distillation under reduced pressure after washing (sic) with anhydrous sodium sulfate and the title compound (1.0 g, 92 %) thereby obtained.

IR spectrum (neat) ν cm^{-1} : 2966, 2895, 1641, 1431, 1119, 1039

NMR spectrum (*$CDCl_3$) δ ppm: 4.10 (4H, s), 3.82-3.75 (2H, m), 3.54 (2H, s), 2.44-2.41 (1H, m), 2.12 (2H, t, J = 5.6 Hz).

Step 3

Synthesis of 4-chloro-1-butanol-3-one

The compound obtained in Step 2 (0.25 g) was dissolved in tetrahydrofuran (10 ml), and 4 N hydrochloric acid (5 ml) was added, and thereafter the mixture was warmed to 50°C on a water bath, stirred for 16 hours, and thereafter extraction with ether. The ethyl acetate layer (sic) was washed with saturated aqueous sodium chloride solution, and after washing (sic) with anhydrous sodium sulfate, the solvent was eliminated by distillation under reduced pressure. The title compound (20 mg, 12 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: hexane : ethyl acetate = 2 : 1).

IR spectrum (neat) ν cm^{-1}= 2939, 2895, 1732, 1398, 1051, 770

NMR spectrum (*$CDCl_3$) δ ppm: 4.14 (2H, s), 3.95-3.89 (2H, m), 2.87 (2H, t, J = 5.4 Hz), 2.23-2.21 (1H, m).

Step 4

Synthesis of 10-bromo-2-(4-hydroxy-2-oxobutyloxy)-5-(3-pyridyl methyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Example 26, the title compound (81 mg, 29 %) was obtained from 10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (40 mg) and the compound obtained in Step 4 (15 mg).

Example 33

Synthesis of 10-bromo-2-ethoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk) carbazol-4-one

To a 20 ml dimethylsulfoxide suspension of 10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (0.3 g) obtained in Example 2 was added potassium carbonate (0.2 g) and the mixture stirred at room temperature for 30 minutes, and thereafter ethyl iodide (0.13 ml) was added and the mixture stirred at 80°C on a warm bath for six hours. The reaction liquor was discharged into iced water and was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, and after washing (sic) with anhydrous sodium sulfate, the solvent was eliminated by distillation under reduced pressure. The title compound (0.16 g, 45 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: ethyl acetate).

Example 34

Synthesis of 10-bromo-2-butoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (0.3 g) obtained in Example 2 was suspended in 30 ml dimethylsulfoxide, and potassium carbonate (0.2 g) was added and the mixture stirred at room temperature for 30 minutes, and thereafter 1-iodo butane (0.1 ml) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water and was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, and after washing (sic) with anhydrous sodium sulfate, the solvent was eliminated by distillation under reduced pressure. The title compound (0.25 g, 73 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: ethyl acetate).

Example 38

Synthesis of 2-acetoxy-10-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (200 mg) obtained in Example 2 was suspended in pyridine (5 ml) and acetic anhydride (0.14 ml) was added and the mixture stirred at room temperature for two hours. A small amount of methanol was added dropwise to the reaction liquor, and thereafter the solvent was eliminated by distillation under reduced pressure and the title compound (100 mg, 46 %) was obtained by washing the crude crystalline residue successively with methanol and ether.

Example 39

Synthesis of 10-bromo-2-(2-oxobutyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (0.3g) obtained in Example 2 was suspended in 20 ml dimethylsulfoxide, and potassium carbonate (0.2 g) was added and the mixture stirred at room temperature for 30 minutes, and thereafter 1-bromo-2-butanone (0.1 ml) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water and the precipitated crystals were recovered by filtration. The title compound (192 mg, 55 %) was obtained by washing the obtained crude crystals successively with methanol and ether.

Example 41

Synthesis of 10-bromo-2-(2-hydroxy pentyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-(2-oxo pentyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (400 mg) obtained in Example 40 was suspended in anhydrous methanol (20 ml) and under ice cooling, sodium borohydride (92 mg) was added a little at a time and the mixture stirred at room temperature for 12 hours. The solvent was eliminated by distillation under the reduced pressure, and thereafter water and methylene chloride were added and extraction was carried out. The methylene chloride layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under the reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: 4 % methanol-containing methylene chloride) and the title compound (140 mg, 28 %) was obtained.

Example 43

Synthesis of 10-bromo-2-(N-ethyl carbamoylmethyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-carboxymethyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (300 mg) obtained in Example 6 was suspended in anhydrous benzene (10 ml), and thionyl chloride (1 ml) was added and the mixture heated under reflux under an argon atmosphere for 3 hours. The solvent was eliminated by distillation under reduced pressure, and the residue thereby obtained was added at room temperature to a mixed solution of 1N sodium hydroxide (0.6 ml) and ethylamine (5 ml, 70% aqueous solution). The title compound (130 mg, 43 %) was obtained by washing the precipitated crystals successively with water, methanol and ether.

Example 44

Synthesis of 10-bromo-2-(4-morpholino carbonyl methyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-carboxymethyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (1 g) obtained in Example 6 was suspended in anhydrous benzene (30 ml), and thionyl chloride (3 ml) was added and the mixture heated under reflux under an argon atmosphere for 3 hours. The solvent was eliminated by distillation under reduced pressure, and the residue thereby obtained was dissolved in anhydrous methylene chloride (50 ml) and was added at room temperature in a mixed solution of morpholine (0.2 ml) and triethylamine (0.3 ml). After stirring for 30 minutes, water and ethyl acetate were added and extraction was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (260 mg, 51 %) was obtained by recrystallizing the crude crystals of residue with ethanol.

Example 46

Synthesis of 10-bromo-2-(4-carboxy-1-piperidino carbonyl methyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-(4-ethoxycarbonyl-1-piperidino carbonyl methyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) obtained in Example 45 was suspended in 30 ml ethanol, and 1N sodium hydroxide aqueous solution (8 ml) was added and the mixture stirred at room temperature for 90 minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter water and ethyl acetate were added, and extraction was carried out. 1 N hydrochloric acid was added to the

aqueous layer and the pH was adjusted to pH 6, and thereafter extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: methylene chloride : methanol = 5 : 1), and thereafter the title compound (100 mg, 42 %) was obtained by washing the crude purified material with ether and recovering by filtration.

Example 47

Synthesis of 10-bromo-2-(N-hydroxymethyl carbamoylmethyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) obtained in Example 2 was suspended in 20 ml dimethylsulfoxide, and potassium carbonate (213 mg) was added and the mixture stirred at room temperature for 30 minutes. Thereafter, N-hydroxymethyl-2-chloroacetamide (130 mg) and potassium iodide (1 tablet) were added and the mixture was stirred at room temperature for 36 hours. The reaction liquor was discharged into iced water and was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (116 mg, 38 %) was obtained by washing the residue with methanol while heating.

Example 48

Synthesis of 10-bromo-2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one.

Step 1

Synthesis of 3-bromo-6-methoxy carbazole-N-α-methyl-β-propionic acid

3-bromo-6-methoxy carbazole (20 g) obtained in Step 1 of Example 1 was dissolved in anhydrous tetrahydrofuran (200 ml) and thereafter, methyl methacrylate (77.6 ml) and then Triton B (0.7 ml) were added and the mixture was heated under reflux under an argon atmosphere for two hours. The solvent was eliminated by distillation under reduced pressure, and the thereby obtained residue was suspended in 60 ml methanol, and sodium hydroxide (6.4 g) dissolved in water (80 ml) at room temperature was added dropwise and the mixture stirred at room temperature for 12 hours. The solvent was eliminated under reduced pressure, and thereafter water and ether were added and liquid separation was caused. 4 N hydrochloric acid was added to the aqueous layer and the aqueous layer

made acidic. Thereafter, ethyl acetate was added and liquid separation was carried out, and the ethyl acetate layer was washed with water and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The crude crystals of the residue were washed with hexane and ether and the title compound (25.0 g, 95 %) was obtained by recovering by filtration.

mp.: 183.4-186.0°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3420, 2950, 1697, 1491, 800

NMR spectrum (DMSO-d_6) δ ppm: 8.38 (1H, s), 7.80 (1H, s), 7.57-7.49 (3H, m), 7.15-7.08 (1H, m), 4.58 (1H, m), 4.34 (1H, m), 3.84 (3H, s), 3.07-2.88 (1H, m), 1.04 (3H, d, J = 6.4 Hz).

Step 2

Synthesis of 10-bromo-5,6-dihydro-2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

To a toluene (1200 ml) suspension of the compound obtained in Step 1 (30 g) was added diphosphorous pentoxide (20 g) and the mixture heated under reflux for 12 hours under an argon atmosphere (during this procedure, fresh diphosphorous pentoxide (20 g) was added twice). The reaction liquor was discharged into ice water (1000 ml) after allowing to cool, and the floating material was separated by filtration using celite. Thereafter, extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel column chromatography (eluting solvent: hexane : ethyl acetate = 5 : 1) and thereafter the title compound (16.0 g, 56 %) was obtained by recrystallizing the crude purified material from ethanol and recovering by filtration.

mp.: 163.8-166.6°C

IR spectrum (KBr tablet) ν cm^{-1}: 1687, 1672, 1497, 1479, 1444, 1194, 797

NMR spectrum (DMSO-d_6) δ ppm: 8.47 (1H, s), 8.12 (1H, d, J = 1.5 Hz), 7.76-7.58 (2H, m), 7.36 (1H, d, J = 1.5 Hz), 4.77 (1H, dd, J = 11.8, 6.5 Hz), 4.06 (1H, dd, J = 11.8, 11.8 Hz), 3.87 (3H, s), 3.32-3.23 (1H, m), 1.28 (3H, d, J = 6.5 Hz).

Step 3

Synthesis of 10-bromo-2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 2 (5.9 g) was dissolved in anhydrous dioxane (400 ml) and DDQ (5.8 g) was added at room temperature and thereafter the mixture was heated under reflux under an argon atmosphere for 23 hours (during this procedure, fresh DDQ (2 g) was added twice). After

allowing to cool, the reaction liquor was added to 1N sodium hydroxide aqueous solution (500 ml) and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed successively with 1N sodium hydroxide aqueous solution and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The obtained crude crystals were washed by heating with 60 ml methanol and the title compound (4.8 g, 82 %) was obtained by recovering by filtration.

Example 49

Synthesis of 10-bromo-2-hydroxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

Boron tribromide (25 g) was added dropwise at room temperature to an anhydrous methylene chloride (400 ml) suspension of 10-bromo-2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (4.8 g) obtained in Example 48, and the mixture was stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (1500 ml) and the precipitated crystals were recovered by filtration. The title compound (4.6 g, quantitatively) was obtained by washing the obtained crude crystals with ether and recovering by filtration.

Example 50

Synthesis of 10-bromo-2-t-butoxycarbonyl methyloxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

To a 10 ml dimethylsulfoxide suspension of 10-bromo-2-hydroxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) obtained in Example 49 was added potassium carbonate (210 mg) and the mixture was stirred at room temperature for 30 minutes. Thereafter, bromoacetic acid t-butyl ester (0.13 ml) was added and the mixture stirred at room temperature for two hours 30 minutes. The reaction liquor was discharged into iced water (50 ml) and extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel column chromatography (eluting solvent: 2 % methanol-containing methylene chloride) and thereafter the crude purified material was washed with ether, and the title compound (130 mg, 39 %) was obtained by recovering by filtration.

Example 51

Synthesis of 10-bromo-5-methyl-2-i-propoxy carbonyl methyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

To a 10 ml dimethylsulfoxide suspension of 10-bromo-2-hydroxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) obtained in Example 49 was added potassium carbonate (210 mg), and the mixture stirred at room temperature for 30 minutes Thereafter, bromoacetic acid i-propyl ester (0.12 ml) and potassium iodide (1 tablet) were added successively and the mixture was stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (50 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: ethyl acetate) and thereafter the crude purified material was washed with ether, and the title compound (220 mg, 67 %) was obtained by recovering by filtration.

Example 52

Synthesis of 10-bromo-2-ethoxycarbonylmethyloxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-methyl-4H-pyrido [3,2,1-jk] carbazole-4-one (400 mg) obtained in Example 49 was suspended in 10 ml dimethylsulfoxide, and thereto was added potassium carbonate (0.34 g) and the mixture stirred at room temperature for 30 minutes. Thereafter bromoacetic acid ethyl ester (0.16 ml) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (50 ml) and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with water, ethanol and ether, and the title compound (360 mg, 71 %) was obtained by recovering by filtration.

Example 53

Synthesis of 10-bromo-2-carboxymethyloxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-ethoxycarbonylmethyloxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (200 mg) obtained in Example 52 was suspended in a mixed solution of ethanol (10 ml) and methylene chloride (10 ml), and thereto was added 1N sodium hydroxide aqueous solution (1 ml) and the mixture stirred at room temperature for 90 minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter the pH was adjusted to pH 1 by the addition of water and 1 N hydrochloric acid, and thereafter the title compound (170 mg, 91 %) was obtained by recovering the precipitated crystals by filtration.

Example 54

Synthesis of 10-bromo-5-methyl-2-(3-pyridylmethyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (350 mg) obtained in Example 49 was suspended in 14 ml dimethylsulfoxide, and potassium carbonate (440 mg) was added and the mixture stirred at room temperature for 30 minutes. Thereafter 3-picolyl chloride hydrochloride (190 mg) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (500 ml) and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with methanol and ether, and the title compound (270 mg, 60 %) was obtained by recovering by filtration.

Example 55

Synthesis of 10-bromo-2-(4-hydroxybutyloxy)-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) obtained in Example 49 was suspended in 10 ml dimethylsulfoxide, and potassium carbonate (210 mg) was added and the mixture stirred at room temperature for 30 minutes. Thereafter, 4-chloro-1-butanol (0.09 ml) was added and the mixture was stirred for 14 hours while adjusting the temperature to 80°C on a warm bath. The reaction liquor was discharged into iced water (500 ml) and extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (80 mg, 26 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: 4 % methanol-containing methylene chloride).

Example 56

Synthesis of 2-acetoxy-10-bromo-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (200 mg) obtained in Example 49 was suspended in pyridine (6 ml), and acetic anhydride (0.18 ml) was added and the mixture stirred at room temperature for 40 minutes. A small amount of methanol was added dropwise to the reaction liquor, and thereafter the solvent was eliminated by distillation under reduced pressure, and the title compound (160 mg, 70 %) was obtained by washing the residue successively with ethanol and ether.

Example 57

Synthesis of 10-bromo-2-(2-oxo pentyloxy)-5-methyl-4H-pyrido [3,2-1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) obtained in Example 49 was suspended in 10 ml dimethylsulfoxide, and potassium carbonate (210 mg) was added and the mixture stirred at room temperature for 30 minutes. Thereafter, 1-bromo-2-pentanone (188 mg) was added and the mixture was stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (500 ml) and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (150 mg, 48 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: 2 % methanol-containing methylene chloride).

Example 58

Synthesis of 10-bromo-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-5,6-dihydro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (3.6 g) obtained in Step 3 of Example 1 was dissolved in anhydrous dioxane (300 ml), and DDQ (3.0 g) was added at room temperature and thereafter the mixture was heated under reflux under an argon atmosphere for five hours. The reaction liquor was added to 1N sodium hydroxide aqueous solution (500 ml) after allowing to cool, and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed successively with 1N sodium hydroxide aqueous solution and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel column chromatography (eluting solvent: 3 % methanol-containing methylene chloride) and the title compound (2.9 g, 79 %) was obtained.

Example 59

Synthesis of 10-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (3.2 g) obtained in Example 58 was suspended in anhydrous methylene chloride (500 ml), and boron tribromide (25 g) was added dropwise at room temperature and the mixture was stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (1 l), and the precipitated crystals were recovered by filtration. Moreover, the methylene chloride layer of the filtrate was washed with saturated aqueous sodium chloride solution and dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated

by distillation under reduced pressure. The thereby obtained two species of mixed crystals were combined and a reaction was carried out in the same way once again. The reaction liquor was discharged into iced water (1 l) and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed by heating with a chloroform • methanol mixed solution and the title compound (2.4 g, 78 %) was obtained by recovering by filtration.

Example 60

Synthesis of 10-bromo-2-t-butoxy carbonyl methyloxy-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one (2.5g) obtained in Example 59 was suspended in 120 ml dimethylsulfoxide, and potassium carbonate (2.2 g) was added and the mixture stirred at room temperature for 30 minutes. Thereafter, bromoacetic acid t-butyl ester (1.4 ml) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (900 ml) and the precipitated crystals were recovered by filtration. The crude crystals were refined by silica gel flash column chromatography (elution solvent; 2 % methanol-containing methylene chloride) and the title compound (1.9 g, 68 %) was obtained.

Example 61

Synthesis of 10-bromo-2-i-propoxy carbonyl methyloxy-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one (3 g) obtained in Example 59 was suspended in 120 ml dimethylsulfoxide, and potassium carbonate (2.6 g) added and the mixture stirred at room temperature for 30 minutes. Thereafter, bromoacetic acid i-propyl ester (1.4 ml) and potassium iodide (1 tablet) were successively added and the mixture was stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (500 ml) and the precipitated crystals were recovered by filtration. The crude crystals were refined by silica gel flash column chromatography (eluting solvent: 1 % methanol-containing methylene chloride) and the title compound (2.0 g, 51 %) thereby obtained.

Example 62

Synthesis of 10-bromo-2-ethoxy carbonyl methyloxy-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one (400 mg) obtained in Example 59 was suspended in 10 ml dimethylsulfoxide, and potassium carbonate (0.34 g) was added and the mixture stirred at room temperature for 30 minutes. Thereafter, bromoacetic acid ethyl ester (0.15 ml) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged

into iced water (50 ml) and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with water, ethanol and ether, and the title compound (410 mg, 84 %) was obtained by recovering by filtration.

Example 63

Synthesis of 10-bromo-2-carboxymethyloxy-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-ethoxycarbonylmethyl oxo-4H-pyrido [3,2,1-jk] carbazol-4-one (200 mg) obtained in Example 62 was suspended in a mixed solution of ethanol (10 ml) and methylene chloride (10 ml), and 1N sodium hydroxide aqueous solution (1 ml) was added and the mixture stirred at room temperature for ten minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter the pH was adjusted to pH 1 by the addition of water and 1 N hydrochloric acid, and thereafter the title compound (160 mg, 84 %) was obtained by recovering the precipitated crystals by filtration.

Example 64

Synthesis of 10-bromo-2-(3-pyridylmethyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one (300 mg) obtained in Example 59 was suspended in 20 ml dimethylsulfoxide, and potassium carbonate (400 mg) was added and the mixture stirred at room temperature for 30 minutes. Thereafter, 3-picolyl chloride hydrochloride (180 mg) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (100 ml) and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with methanol and ether, and the title compound (200 mg, 52 %) was obtained by recovering by filtration.

Example 70

Synthesis of 10-bromo-2-(5-hydroxymethyl-3-pyridylmethyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

2-(5-acetoxymethyl-3-pyridylmethyloxy)-10-bromo-4H-pyrido [3,2,1-jk] carbazol-4-one (200 mg) obtained in Example 69 was suspended in 12 ml methanol, and a solution comprising sodium hydroxide 100 mg dissolved in water 0.8 ml was added, and the mixture was stirred at room temperature for 1 hour. The precipitated crystals were washed successively with methanol and ether, and the title compound (170 mg, 93 %) was obtained by recovering by filtration.

Example 71

Synthesis of 2-(6-acetoxymethyl-2-pyridylmethyloxy)-10-bromo-4H-pyrido [3,2,1-jk] carbazol-4-one.

Step 1

Synthesis of pyridine-2,6-dimethanol mono acetate

Pyridine-2,6-dimethanol (5 g) was suspended in 10 ml pyridine, and acetyl chloride (2.56 ml) was added dropwise at room temperature and the mixture stirred at room temperature for 20 minutes. The solvent was eliminated by distillation under reduced pressure. The title compound (2 g, 31 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: chloroform : methanol = 9 : 1).

IR spectrum (neat) ν cm^{-1}: 1741, 1599, 1462, 1377, 1228, 1074, 793

NMR spectrum (*DMSO-d_6) δ ppm: 7.82 (1H, t, J = 7.7 Hz), 7.41 (1H, d, J = 7.7 Hz), 7.26 (1H, d, J = 7.7 Hz), 5.45 (1H, t, J = 5.8 Hz), 5.10 (2H, s), 4.55 (2H, d, J = 5.8 Hz), 2.12 (3H, s).

Step 2

Synthesis of 2-acetoxymethyl-6-chloromethyl pyridine

The compound (1.9 g) obtained in Step 1 was suspended in anhydrous benzene (10 ml), and thionyl chloride (0.77 ml) was added dropwise at room temperature and the mixture stirred for 20 minutes. The solvent was eliminated by distillation under reduced pressure, and the title compound (1.29 g, 62 %) was obtained by washing the residue with ether.

IR spectrum (neat) ν cm^{-1}: 2953, 1743, 1595, 1460, 1375, 1227, 1057

NMR spectrum (*DMSO-d_6) δ ppm: 7.88 (1H, t, J = 7.6 Hz), 7.50 (1H, d, J = 7.6 Hz), 7.39 (1H, d, J = 7.6 Hz), 5.14 (2H, s), 4.78 (2H, s), 2.13 (3H, s).

Step 3

Synthesis of 2-(6-acetoxymethyl-2-pyridyl methyloxy)-10-bromo-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Example 64, the title compound (480 mg, 79 %) was obtained from 10-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one (400 mg) and the compound (280 mg) obtained in Step 3.

Example 73

Synthesis of 10-bromo-2-(5-methoxycarbonyl-2-pyridylmethyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one.

Step 1

Synthesis of 6-bromomethyl nicotinic acid methyl ester

To 6-methyl methylnicotinate (1 g) dissolved in carbon tetrachloride (100 ml) was added N-bromo succinimide (1.3 g) and the mixture heated under reflux for 8 hours under an argon atmosphere. After allowing to cool, the precipitated crystals were recovered by filtration and the solvent was eliminated from the filtrate by distillation under reduced pressure. The title compound (540 mg, 35 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: hexane : methylene chloride = 1 : 3).

mp.: 75.2-76.3°C

IR spectrum (KBr tablet) ν cm^{-1}: 1728, 1713, 1595, 1435, 1286, 1124, 1103

NMR spectrum (*DMSO-d_6) δ ppm: 9.05 (1H, s), 8.34-8.30 (1H, m), 7.71 (1H, d, J = 7.9 Hz), 4.77 (2H, s), 3.89 (3H, s).

Step 2

Synthesis of 10-bromo-2-(5-methoxycarbonyl-2-pyridylmethyl oxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Example 64, the title compound (250 mg, 67 %) was obtained from 10-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) and the compound (220 mg) obtained in Step 1.

Example 74

Synthesis of 10-bromo-2-(5-methyl-3-pyridylmethyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

To lutidine (1 g) dissolved in 100 ml carbon tetrachloride was added N-bromo succinimide (1.3 g) and the mixture was heated under reflux under an argon atmosphere for five hours. After allowing to cool, the crystals which precipitated were separated by filtration. By using the thereby obtained filtrate, the title compound (20 mg, 15 %) was obtained from 10-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one (100 mg) in accordance with Example 64.

Example 75

Synthesis of 10-bromo-2-pyrazyl methyloxy-4H-pyrido [3,2,1-jk] carbazol-4-one

Pyrazine-2-carboxylic acid (2 g) was suspended in a mixed solvent of anhydrous methanol (100 ml) and anhydrous tetrahydrofuran (50 ml), and trimethylsilyldiazomethane hexane solution (10 ml) was added under ice cooling, and the mixture was stirred at room temperature for 12 hours. After eliminating the solvent by distillation under reduced pressure, the thereby obtained residue was suspended in anhydrous tetrahydrofuran (15 ml) and lithium aluminium hydride (530 mg) was gradually added at room temperature. After stirring for two hours, saturated sodium bicarbonate was added to the reaction liquor till there was no more effervescence, and extraction was carried out with ether. The ether layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel column chromatography (eluting solvent: methylene chloride : methanol = 10 : 1). The thereby obtained compound (200 mg) was suspended in anhydrous benzene (10 ml), and thionyl chloride (an excess quantity) was added dropwise at room temperature and the mixture stirred for 20 minutes. The solvent was eliminated by distillation under reduced pressure. By using the thereby obtained residue, the title compound (40 mg, 10 %) was obtained from 10-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one (300 mg) in accordance with Example 64.

Example 79

Synthesis of 10-bromo-2-(4-hydroxybutyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

To a 12 ml dimethylsulfoxide suspension of 10-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) obtained in Example 59 was added potassium carbonate (220 mg), and after stirring at room temperature for 30 minutes, 4-chloro-1-butanol (0.095 ml) and potassium iodide (1 tablet) were added, and the mixture stirred for 24 hours while adjusting the temperature to 80°C on a warm bath. The reaction liquor was discharged into iced water (100 ml) and extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (160 mg, 52 %) was obtained by refining the residue with silica gel flash column chromatography (eluting solvent : methylene chloride : methanol = 20 : 1).

Example 83

Synthesis of 10-bromo-2-(2-oxo pentyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-4H-pyrido [3,2-1-jk] carbazol-4-one (250 mg) obtained in Example 59 was suspended in dimethylsulfoxide (10 ml), and thereto was added potassium carbonate (210 mg). After stirring at room temperature for 30 minutes, 1-bromo-2-pentanone (170 mg) was added and the mixture stirred at room temperature for 3 hours. The reaction liquor was discharged into iced water and extraction carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (130 mg, 41 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: 2 % methanol-containing methylene chloride).

Example 84

Synthesis of 10-bromo-2-methoxy-5-(2-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-5,6-dihydro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (0.7 g) obtained in Step 3 of Example 1 was suspended in 30 ml ethanol, and thereto were added at room temperature pyridine-2-aldehyde (0.7 g) and sodium hydroxide (0.3 g) dissolved in water (5 ml), and the mixture was stirred at room temperature for 12 hours. The solvent was eliminated by distillation under reduced pressure to about half the quantity, and thereafter, the crystals which had precipitated were recovered by filtration, washed successively with water, ethanol and ether, and the title compound (0.56 g, 61 %) thereby obtained.

Example 85

Synthesis of 10-bromo-2-hydroxy-5-(2-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-methoxy-5-(2-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (0.54 g) obtained in Example 84 was suspended in anhydrous methylene chloride (30 ml), and thereto was added dropwise at room temperature boron tribromide (5 ml) and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water, and thereto was added saturated sodium carbonate aqueous solution until there was no more effervescence, and the precipitated crystals were recovered by filtration. The title compound (0.173 g, 33 %) was obtained by washing the obtained crude crystals with a methylene chloride • methanol mixed solution.

Example 86

Synthesis of 10-bromo-2-t-butoxycarbonyl methyloxy-5-(2-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(2-pyridyl methyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (190 mg) obtained in Example 85 was suspended in 10 ml dimethylsulfoxide, and thereto was added potassium carbonate (130 mg). After stirring at room temperature for 30 minutes, bromoacetic acid t-butyl ester (110 mg) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water and extraction carried out with methylene chloride. The methylene chloride layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (88 mg, 36 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: 3 % methanol-containing methylene chloride).

Example 95

Synthesis of 10-bromo-2-methoxy-5-(1H-1,2,4-triazol-1-ylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (400 mg) obtained in Example 48 was suspended in anhydrous benzene, and thereto were added N-bromo succinimide (312 mg) and 2,2'-azobisisobutyronitrile (1 tablet), and the mixture was heated under reflux under argon for 1 hour. After allowing to cool, the solvent was eliminated by distillation under reduced pressure. This was added to 1,2,4-triazole (94 mg) and cesium carbonate (443 mg) suspended in anhydrous acetonitrile (20 ml) and the mixture was stirred at room temperature for 12 hours. The solvent was eliminated under reduced pressure and thereafter, water and methylene chloride were added and extraction carried out. The methylene chloride layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (60 mg, 12 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: 3 % methanol-containing methylene chloride).

Example 97

Synthesis of 2-acetoxy-10-bromo-5-(1H-1,2,4-triazol-1-yl methyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-bromo-2-hydroxy-5-(1H-1,2,4-triazol-1-yl methyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (30 mg) obtained in Example 96 was suspended in 0.8 ml pyridine, and thereto was added acetic anhydride (0.021 ml) and the mixture was stirred at room temperature for 3 hours. A small amount of methanol was added dropwise to the reaction liquor, and thereafter the solvent was eliminated by distillation under reduced pressure, and the title compound (24 mg, 72 %) was obtained by washing the residue successively with ethanol and ether.

Example 98

Synthesis of 10-bromo-5-ethoxycarbonyl-2-methoxy-4H-pyrido [3,2-1-jk] carbazol-4-one

Step 1

Synthesis of 3-bromo-6-methoxy carbazole-N-methylene malonic acid diethyl ester

The compound 3-bromo-6-methoxy carbazole (2.5 g) obtained in Step 1 of Example 1 and ethoxymethylene malonic acid diethyl ester (9.16 ml) were dissolved in xylene and the solution heated under reflux under an argon atmosphere for 120 hours. The solvent was eliminated by distillation under reduced pressure after allowing to cool. By refining the residue by silica gel column chromatography (eluting solvent: chloroform), the title compound (2 g, 50 %) was obtained.

mp.: 95.6-97.6°C

IR spectrum (KBr tablet) ν cm^{-1}: 1716, 1705, 1491, 1246, 1221, 791

NMR spectrum (DMSO-d_6) δ ppm: 8.50 (1H, d, J = 2.0 Hz), 8.43 (1H, s), 7.89 (1H, d, J = 2.6 Hz), 7.65 (1H, dd, J = 8.9, 2.0 Hz), 7.54-7.41 (2H, m), 7.14 (1H, dd, J = 8.9, 2.6 Hz), 4.29 (2H, q, J = 7.1 Hz), 4.00 (2H, q, J = 7.1Hz), 3.87 (3H, s), 1.31 (3H, t, J = 7.1 Hz), 0.9 (3H, t, J = 7.1 Hz).

Step 2

Synthesis of 10-bromo-5-ethoxycarbonyl-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound (1.9 g) obtained in Step 1 was added to polyphosphoric acid (140 g) and the mixture was stirred for 11 hours while maintaining a temperature of 80°C on a warm bath. After allowing to cool, the reaction liquor was discharged into iced water and extraction carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced

pressure. The title compound (650 mg, 38 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: chloroform).

Example 99

Synthesis of 10-bromo-5-carboxy-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

To a 10 ml ethanol suspension of 10-bromo-5-ethoxycarbonyl-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (400 mg) obtained in Example 98 was added 1N sodium hydroxide (3 ml) and the mixture stirred at room temperature for 12 hours. The solvent was eliminated by distillation under reduced pressure, and thereafter the pH was adjusted to pH 1 by the addition of 1N hydrochloric acid. The thereby precipitated crystals were recovered by filtration and the title compound (310 mg, 83 %) was obtained by washing with ethanol and ether.

Example 100

Synthesis of 10-bromo-2-methoxy-5-(4-morpholino carbonyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

To an anhydrous benzene (10 ml) suspension of 10-bromo-5-carboxy-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (180 mg) obtained in Example 99 was added thionyl chloride (0.71 ml) and the mixture was heated under reflux under an argon atmosphere for five hours. The solvent was eliminated by distillation under reduced pressure, and the thereby obtained residue was added at room temperature to a mixed solution of morpholine (0.098 ml) and triethylamine (0.157 ml) dissolved in anhydrous methylene chloride (10 ml). After stirring for two hours, water and methylene chloride were added and extraction was carried out. The methylene chloride layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (165 mg, 77 %) was obtained by washing the residue successively with ethanol and ether.

Example 101

Synthesis of 9-bromo-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 4'-bromo-2' nitrophenyl benzoquinone

4-bromo-2-nitroaniline (10 g) suspended in a mixed solution of concentrated hydrochloric acid (120 ml) and water (22 ml) was caused to dissolve by heating using a warm water bath, and on completion of thorough dissolution, the internal temperature was lowered to 10°C and the solution stirred for 30

minutes. Sodium nitrite (5.3 g) dissolved in water (15 ml) was added dropwise so as not to exceed an internal temperature of 10°C. The insolubles were separated by filtration using glass wool, and thereafter the liquid residue was added slowly dropwise at room temperature to an aqueous suspension (56.7 ml) of sodium bicarbonate (56.8 g) and benzoquinone (5.6 g), and the thereby precipitated crystals were recovered by filtration. The obtained crude crystals were washed with ethanol, and the title compound (8.6 g, 60 %) was obtained by recovering by filtration.

mp.: 164.1-168.7°C.

IR spectrum (KBr tablet) ν cm^{-1}: 1664, 1651, 1603, 1524, 1354, 1101, 918

NMR spectrum (*DMSO-d_6) δ ppm: 8.40 (1H, d, J = 2.0 Hz), 8.14 (1H, dd, J = 8.1, 2.0 Hz), 7.59 (1H, d, J = 8.1 Hz), 7.13 (1H, s), 7.03 (2H, s).

Step 2

Synthesis of 2'-amino-4'-bromo phenyl hydroquinone

The compound obtained in Step 1 (8.5 g) was suspended in 3N hydrochloric acid (213 ml) and thereafter tin chloride dihydrate (25 g) was added and the mixture stirred for two hours on a warm bath at 90°C. After allowing to cool, the mixture was discharged into water (300 ml) and the pH was adjusted to pH 7 with 3N sodium hydroxide aqueous solution, and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The obtained crude purified material was washed with ether, and the title compound (4.8 g, 61 %) was obtained by recovering by filtration.

mp.: 203.4-206.5°C

IR spectrum (KBr tablet) ν cm^{-1}: 3388, 1616, 1506, 1479, 1406, 1244, 1211, 779

NMR spectrum (*DMSO-d_6) δ ppm: 8.87 (1H, s), 8.80 (1H, s), 6.90 (1H, d, J = 2.0 Hz), 6.84 (1H, d, J = 8.5 Hz), 6.74 (1H, d, J = 2.0 Hz), 6.71 (1H, d, J = 1.4 Hz), 6.58 (1H, dd, J = 8.5, 3.0 Hz), 6.46 (1H, d, J = 3.0 Hz), 4.87 (2H, s).

Step 3

Synthesis of 2-bromo-6-hydroxycarbazole

The compound obtained in Step 2 (14 g) was dissolved in methanol, and silica gel (90 g) was added, and the solvent was eliminated by distillation under reduced pressure. The mixture was stirred on a warm bath at 90°C for ten hours. Elution was caused using methanol and the silica gel used in reaction was separated by filtration. The filtrate was concentrated down by distillation under reduced pressure

and the residue was refined by silica gel column chromatography (eluting solvent: hexane : ethyl acetate = 1 : 1) and the title compound (5.0 g, 38 %) thereby obtained.

mp.: 248.4-252.2°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3402, 1608, 1583, 1458, 1178, 812, 609.

NMR spectrum (*DMSO-d white) δ ppm: 11.06 (1H, s), 9.02 (1H, s), 7.95 (1H, d, J = 8.2 Hz), 7.58 (1H, d, J = 1.7 Hz), 7.42 (1H, d, J = 2.4 Hz), 7.31 (1H, d, J = 8.7 Hz), 7.20 (1H, dd, J = 8.2, 1.7 Hz), 6.92 (1H, dd, J = 8.7, 2.4 Hz).

Step 4

Synthesis of 2-bromo-6-methoxy carbazole

To the compound obtained in Step 3 (6 g) dissolved in 180 ml acetone was added potassium hydroxide (1.3 g) at room temperature, and thereafter, dimethyl sulfate (2.2 ml) was added dropwise. After stirring at room temperature for two hours, the solvent was eliminated by distillation and extraction with water and ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: hexane : ethyl acetate = 4 : 1) and the title compound (3.2 g, 51 %) thereby obtained.

mp.: 138.6-142.6°C

IR spectrum (KBr tablet) ν cm^{-1}: 3336, 1495, 1219, 1201, 804

NMR spectrum (*DMSO-d_6) δ ppm: 11.19 (1H, s), 8.04 (1H, d, J = 8.3 Hz), 7.69 (1H, d, J = 2.5 Hz), 7.61 (1H, d, J = 1.7 Hz), 7.40 (1H, d, J = 8.7 Hz), 7.23 (1H, dd, J = 8.3, 1.7 Hz), 7.04 (1H, dd, J = 8.7, 2.5 Hz), 3.83 (3H, s).

Step 5

Synthesis of 2-bromo-6-methoxy carbazole-N-β-propionic acid

To a 50 ml acetone suspension of the compound obtained in Step 4 (2.8 g) were added dropwise at room temperature methyl acrylate (1.8 ml) and then Triton B (0.6 ml). After stirring for 40 minutes, the solvent was eliminated by distillation under reduced pressure. The thereby obtained residue was dissolved in 50 ml methanol, and thereto was added dropwise at room temperature sodium hydroxide (0.9 g) dissolved in water (10 ml), and the mixture was stirred at room temperature for 70 minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter the pH was adjusted to pH 3 with 1N hydrochloric acid and extraction with ethyl acetate was carried out. The

ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was washed with hexane and the title compound thereby recovered by filtration (3.2 g, 91 %).

mp.: 169.0-171.9°C

IR spectrum (KBr tablet) ν cm^{-1}: 1693, 1489, 1483, 1290, 1225, 1209, 874

NMR spectrum (*DMSO-d_6) δ ppm: 12.39 (1H, s), 8.08 (1H, d, J = 8.2 Hz), 7.86 (1H, d, J = 1.6 Hz), 7.74 (1H, d, J = 2.6 Hz), 7.55 (1H, d, J = 8.9 Hz), 7.29 (1H, dd, J = 8.2, 1.6 Hz), 7.12 (1H, dd, J = 8.9, 2.6 Hz), 4.58 (2H, t, J = 6.8 Hz), 3.85 (3H, s), 2.71 (2H, t, J = 6.8 Hz).

Step 6

Synthesis of 9-bromo-5,6-dihydro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

To an anhydrous chloroform (100 ml) suspension of the compound obtained in Step 5 (2.9 g) was added at room temperature PPE (21.6 g) dissolved in anhydrous chloroform (100 ml), and the mixture was heated under reflux under an argon atmosphere for 1 hour. This was discharged into water (300 ml) after allowing to cool, and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel column chromatography (eluting solvent: hexane : ethyl acetate = 9 : 1) and the title compound (1.7 g, 63 %) thereby obtained.

mp.: 174.9-178.8°C

IR spectrum (KBr tablet) ν cm^{-1}: 1666, 1479, 1298, 1223, 1201, 1032, 797

NMR spectrum (*DMSO-d_6) δ ppm: 8.17 (1H, d, J = 8.4 Hz), 8.10 (1H, d, J = 2.4 Hz), 7.95 (1H, d, J = 1.8 Hz), 7.40 (1H, dd, J = 8.4, 1.8 Hz), 7.36 (1H, d, J = 2.4 Hz), 4.56 (2H, t, J = 7.1 Hz), 3.88 (3H, s), 3.12 (2H, t, J = 7.1 Hz).

Step 7

Synthesis of 9-bromo-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 6 (3.7 g) was suspended in 210 ml ethanol, and thereto were added at room temperature pyridine-3-aldehyde (1.7 ml) and sodium hydroxide (3.6 g) dissolved in water (20 ml), and the mixture was stirred at room temperature for 12 hours. The solvent was eliminated by distillation under reduced pressure to about half the quantity, and thereafter the precipitated crystals were recovered by filtration, washed successively with water, ethanol and ether, and the title compound (4.2 g, 90 %) thereby obtained.

Example 102

Synthesis of 9-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

9-bromo-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (700 mg) obtained in Example 101 was suspended in anhydrous methylene chloride (70 ml), boron tribromide methylene chloride solution (1M; 10 ml) was added dropwise at room temperature, and the mixture was stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (100 ml) and thereto was added saturated sodium carbonate aqueous solution until there was no more effervescence, and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with ethanol and ether and the title compound (450 mg, 67 %) thereby obtained.

Example 103

Synthesis of 9-bromo-2-t-butoxycarbonyl methyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

9-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (200 mg) obtained in Example 102 was suspended in dimethylsulfoxide (8 ml), and thereto was added potassium carbonate (136 mg) and the mixture stirred at room temperature for 30 minutes. Thereafter, bromoacetic acid t-butyl ester (0.09 ml) was added and the mixture stirred at room temperature for two hours. The reaction liquor was discharged into iced water (20 ml) and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with water, ethanol and ether, and the title compound (144 mg, 56 %) thereby obtained by recovering by filtration.

Example 104

Synthesis of 9-bromo-2-carboxymethyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

9-bromo-2-t-butoxycarbonyl methyloxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (57 mg) obtained in Example 103 was dissolved in acetic acid (0.5 ml) and 48 % HBr (0.5 ml), and the mixture was stirred at 60°C for 1 hour. After allowing to cool, the pH was adjusted to pH7 with saturated sodium bicarbonate. The precipitated crystals were recovered by filtration, washed successively with water, ethanol and ether, and the title compound (40 mg, 79 %) was obtained by recovering by filtration.

Example 105

Synthesis of 9-bromo-5-(3-pyridylmethyl)-2-(3-pyridylmethyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

9-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (200 mg) obtained in Example 102 was suspended in dimethylsulfoxide (8 ml), potassium carbonate (204 mg) was added and the mixture stirred at room temperature for 30 minutes Thereafter, 3-picolyl chloride (0.09 ml) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (20 ml) and the precipitated crystals recovered by filtration. The obtained crude crystals were washed successively with water, ethanol and ether, and the title compound (177 mg, 72 %) obtained by recovering by filtration.

Example 107

Synthesis of 9-bromo-2-(5-hydroxymethyl-3-pyridylmethyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

2-(5-acetoxymethyl-3-pyridylmethyloxy)-9-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (200 mg) obtained in Example 106 was suspended in 10 ml methanol, thereto was added a solution comprising sodium hydroxide 85 mg dissolved in water 0.8 ml, and the mixture was stirred at room temperature for ten minutes. The precipitated crystals were recovered by filtration, washed successively with methanol and ether, and the title compound (170 mg, 92 %) was obtained.

Example 108

Synthesis of 9-bromo-5-(3-pyridyl methyl)-2-(5-pyrimidyl methyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one.

Step 1

Synthesis of 5-pyrimidine ethanol

Pyrimidine-5-carboxy aldehyde (400 mg) prepared using a process in accordance with the literature (Syn Commun, 24, 253 (1994)) was dissolved in anhydrous methanol (8 ml), and thereto was added a little at a time sodium boron hydride (210 mg) under ice cooling and the mixture stirred for 30 minutes. The solvent was eliminated by distillation under reduced pressure and extraction carried out with water and ethyl acetate. The ethyl acetate layer was dried with anhydrous sodium sulphate after washing with saturated aqueous sodium chloride solution, and thereafter the solvent was eliminated by distillation under reduced pressure and the title compound (250 mg, 61 %) thereby obtained.

IR spectrum (neat) ν cm^{-1}: 1651, 1570, 1443, 1408, 1036, 725.

NMR spectrum (*$CDCl_3$) δ ppm: 9.17 (1H, s), 8.77 (2H, s), 7.27 (1H, s), 4.79 (2H, s).

Step 2

Synthesis of 5-pyrimidyl methyl chloride

To the compound obtained in Step 1 (270 mg) suspended in anhydrous methylene chloride (10 ml) was added thionyl chloride (10 ml) at room temperature, and the mixture was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure and the title compound (310 mg, 99 %) thereby obtained.

IR spectrum (neat) ν cm^{-1}: 1626, 1589, 1537, 1431, 1410, 1041, 687

NMR spectrum (*DMSO-d_6) δ ppm: 9.18 (1H, s), 8.91 (2H, s), 4.86 (2H, s).

Step 3

Synthesis of 9-bromo-5-(3-pyridylmethyl)-2-(5-pyrimidyl methyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (200 mg, 65 %) was obtained from 9-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) and the 5-pyrimidyl methyl chloride (120 mg) obtained in Step 2 in accordance with Example 105.

Example 109

Synthesis of 9-bromo-2-(N-ethyl carbamoylmethyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (230 mg, 63 %) was obtained from 9-bromo-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (300 mg) and N-ethyl-2-chloroacetamide (153 mg) in accordance with Example 105.

Example 110

Synthesis of 9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

To 9-bromo-2-hydroxy-5-(3-pyridyl methyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (400 mg) obtained in Example 102 suspended in 40 ml dimethylsulfoxide was added potassium carbonate (540 mg) and the mixture stirred at room temperature for 30 minutes. Thereafter, 3-bromo-1-propanol (0.3 ml) was added, and the mixture was stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (100 ml) and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with water, ethanol and ether, and the title compound (177 mg, 72 %) obtained by recovering by filtration.

Example 112

Synthesis of 2-(3-aminopropyloxy)-9-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

To 9-bromo-2-(3-N-phthalimide propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (50 mg) obtained in Example 111 suspended in 0.8 ml methanol was added hydrazine monohydrate (8.45 mg), and the mixture was heated under reflux under an argon atmosphere for 90 minutes. After allowing to cool, water (1 ml) was added. The solvent was eliminated by distillation under reduced pressure, and thereafter, water and ethyl acetate were added and extraction was carried out. The ethyl acetate layer was dried with anhydrous sodium sulphate after washing with saturated aqueous sodium chloride solution, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: methylene chloride : methanol = 10 : 1) and the title compound (39 mg, 67 %) was obtained.

Example 113

Synthesis of 9-bromo-2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 2-bromo-6-methoxy carbazole-N-α-methyl-β-propionic acid

To 2-bromo-6-methoxy carbazole (4 g) obtained in Step 4 of Example 101 dissolved in anhydrous tetrahydrofuran (32 ml) were added methyl methacrylate (12.4 ml) and then Triton B (1.12 ml), and the mixture was heated under reflux under an argon atmosphere for 1 hour. The solvent was eliminated by distillation under reduced pressure, and the residue thereby obtained was suspended in 40 ml methanol. Thereto was added dropwise at room temperature sodium hydroxide (1 g) dissolved in water (13 ml) and the mixture heated under reflux for four hours. The solvent was eliminated under reduced pressure, and thereafter water and ether were added and liquid separation was carried out. The aqueous layer was made acidic by the addition of 1N hydrochloric acid and thereafter extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was washed with hexane and recovered by filtration and the title compound (4.0 g, 95 %) thereby obtained.

NMR spectrum (*DMSO-d_6) δ ppm: 12.39 (1H, bs), 8.07 (1H, d, J = 8.3 Hz), 7.82 (1H, d, J = 1.6 Hz), 7.73 (1H, d, J = 2.4 Hz), 7.53 (1H, d, J = 8.9 Hz), 7.27 (1H, dd, J = 8.3, 1.6 Hz), 7.09 (1H, dd, J = 8.9, 2.4 Hz), 4.61-4.54 (1H, m), 4.38-4.31 (1H, m), 3.84 (3H, s), 3.02-2.95 (1H, m), 1.08 (3H, d, J = 7.0 Hz).

Step 2

Synthesis of 9-bromo-5,6-dihydro-2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

To the compound obtained in Step 1 (4.0 g) suspended in anhydrous chloroform (130 ml) was added at room temperature PPE (28.6 g) dissolved in anhydrous chloroform (130 ml), and the mixture was heated under reflux under an argon atmosphere for 1 hour. The mixture was discharged into water (200 ml) after allowing to cool, and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel column chromatography (eluting solvent: hexane : ethyl acetate = 9 : 1) and the title compound (2.7 g, 71 %) thereby obtained.

mp.: 201.1-204.4°C

IR spectrum (KBr tablet) ν cm^{-1}: 1659, 1477, 1462, 1308, 1225, 1032, 866

NMR spectrum (DMSO-d_6) δ ppm: 8.17 (1H, d, J = 8.3 Hz), 8.09 (1H, d, J = 2.3 Hz), 7.94 (1H, d, J = 1.3 Hz), 7.41-7.36 (2H, m), 4.81 (1H, dd, J = 12.0, 6.6 Hz), 4.10 (1H, dd, J = 12.0, 12.0 Hz), 3.38 (3H, s), 3.32-3.25 (1H, m), 1.28 (3H, d, J = 6.6 Hz).

Step 3

Synthesis of 9-bromo-2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

To the compound obtained in Step 2 (2.7 g) dissolved in anhydrous dioxane (150 ml) was added DDQ (2.67 g) at room temperature, and thereafter the mixture was heated under reflux under an argon atmosphere for nine hours (during this procedure, fresh DDQ (2 g) was added). The reaction liquor was added to 1N sodium hydroxide aqueous solution (300 ml) after allowing to cool, and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The obtained crude crystals were washed by heating with ethanol and recovered by filtration and the title compound (1.7 g, 63 %) thereby obtained.

Example 114

Synthesis of 9-bromo-2-hydroxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

9-bromo-2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (1.6 g) obtained in Example 113 was suspended in anhydrous methylene chloride (120 ml) and a boron tribromide methylene chloride solution (1M; 28 ml) was added dropwise at room temperature, and the mixture was stirred at room temperature for 3 hours. The reaction liquor was discharged into iced water (100 ml) and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with ethanol and ether and the title compound (1.5 g, 98 %) thereby obtained.

Example 115

Synthesis of 9-bromo-5-methyl-2-(3-pyridylmethyloxy)-4H-pyrido [3,2,1-jk] carbazol-4-one

9-bromo-2-hydroxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) obtained in Example 114 was suspended in 10 ml dimethylsulfoxide, and potassium carbonate (315 mg) was added and the mixture stirred at room temperature for 30 minutes. Thereafter, 3-picolyl chloride (137 mg) was added and the mixture stirred at room temperature for 12 hours. The reaction liquor was discharged into iced water (100 ml) and the precipitated crystals recovered by filtration. The obtained crude crystals were washed successively with water, ethanol and ether, and the title compound (250 mg, 78 %) obtained by recovering by filtration.

Example 116

Synthesis of 9-bromo-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

9-bromo-5,6-dihydro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (1.0 g) obtained in Step 6 of Example 101 was dissolved in anhydrous dioxane (40 ml), thereto was added DDQ (1.45 g) at room temperature and thereafter the mixture was heated under reflux under an argon atmosphere for 3 hours. The reaction liquor was added to 1N sodium hydroxide aqueous solution (150 ml) after allowing to cool, and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (0.7 g, 70 %) was obtained by washing the obtained crude crystals with ethanol, and recovering by filtration.

Example 117

Synthesis of 9-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one

9-bromo-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (650 mg) obtained in Example 116 was suspended in anhydrous methylene chloride (50 ml), and thereto was added dropwise at room temperature boron tribromide methylene chloride solution (1M; 12 ml) and the mixture heated under reflux for 14 hours. The reaction liquor was discharged into 1N sodium hydroxide aqueous solution (100 ml) and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with ethanol and ether, and the title compound (380 mg, 61 %) was obtained.

Example 119

Synthesis of 9-bromo-2-carboxymethyloxy-4H-pyrido [3,2,1-jk] carbazol-4-one

9-bromo-2-t-butoxycarbonyl methyloxy-4H-pyrido [3,2,1-jk] carbazol-4-one (120 mg) obtained in Example 118 was dissolved in acetic acid (5 ml) and 48 % HBr (5 ml), and the mixture was stirred at room temperature for 12 hours. The reaction liquor was discharged into water, and the precipitated crystals were recovered by filtration, washed successively with water, ethanol and ether and the title compound (96 mg, 92 %) thereby obtained.

Example 121

Synthesis of 5-benzyl-9-bromo-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

9-bromo-5,6-dihydro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (200 mg) obtained in Step 6 of Example 101 was suspended in 12 ml ethanol, and thereto were added at room temperature benzaldehyde (103 mg) and sodium hydroxide (190 mg) dissolved in water (1 ml), and the mixture was stirred at room temperature for 12 hours. The solvent was eliminated by distillation under reduced pressure to about half the quantity, and thereafter, the crystals which had precipitated were recovered by filtration, washed successively with water, ethanol and ether, and the title compound (217 mg, 87 %) was obtained.

Example 122

Synthesis of 5-benzyl-9-bromo-2-hydroxy-4H-pyrido [3,2,1-jk] carbazol-4-one

5-benzyl-9-bromo-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (137 mg) obtained in Example 121 was dissolved in acetic acid (7 ml) and 48 % HBr (7 ml), and the mixture stirred at room temperature for 30 minutes. The reaction liquor was discharged into water, and the precipitated crystals were recovered by filtration, washed successively with water, ethanol and ether, and the title compound (77 mg, 58 %) thereby obtained.

Example 123

Synthesis of 9-bromo-2-methoxy-5-(5-methyl-3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

To a 18 ml ethanol suspension of 9-bromo-5,6-dihydro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (300 mg) obtained in Step 6 of Example 101 were added at room temperature sodium hydroxide (291 mg) dissolved in water (1.5 ml) and 5-methyl nicotinaldehyde (176 mg) prepared using a process in accordance with the literature (JOC, 53, 3513 (1988)), and the mixture was stirred at

room temperature for 12 hours. The solvent was eliminated by distillation under reduced pressure to about half the quantity, and thereafter, the crystals which had precipitated were recovered by filtration and washed successively with water, ethanol and ether, and the title compound (312 mg, 79 %) thereby obtained.

Example 124

Synthesis of 9-bromo-2-hydroxy-5-(5-methyl-3-pyridylmethyl)-4H-pyrido [3-2,1-jk] carbazol-4-one

9-bromo-2-methoxy-5-(5-methyl-3-pyridylmethyl)-4H-pyrido [3-2,1-jk] carbazol-4-one (302 mg) obtained in Example 123 was suspended in anhydrous methylene chloride (80 ml), and boron tribromide (0.33 ml) was added dropwise at room temperature and the mixture stirred at room temperature for 3 hours. The reaction liquor was discharged into iced water (100 ml) and thereto was added saturated aqueous sodium bicarbonate solution until there was no more effervescence, and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with ethanol and ether and the title compound (227 mg, 78 %) thereby obtained.

Example 125

Synthesis of 9-bromo-2-methoxy-5-(5-pyrimidyl methyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

To a 17 ml ethanol suspension of 9-bromo-5,6-dihydro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one (300 mg) obtained in Step 6 of Example 101 were added at room temperature sodium hydroxide (291 mg) dissolved in water (1.7 ml) and pyrimidine-5-carboxy aldehyde (157 mg) prepared using a process in accordance with the literature (Syn Commun, 24, 253 (1994)), and the mixture was stirred at room temperature for 12 hours. The solvent was eliminated by distillation under reduced pressure to about half the quantity, and thereafter the precipitated crystals were recovered by filtration. The title compound (300 mg, 79 %) was obtained by refining the residue by alumina flash column chromatography (eluting solvent: 4 % methanol-containing methylene chloride).

Example 126

Synthesis of 9-bromo-2-hydroxy-5-(5-pyrimidyl methyl)-4H-pyrido [3,2,1-jk) carbazol-4-one

9-bromo-2-methoxy-5-(5-pyrimidyl methyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (260 mg) obtained in Example 125 was suspended in anhydrous methylene chloride (16 ml) and boron tribromide (3.7 ml) was added dropwise at room temperature, and the mixture was stirred at room temperature for 3 hours. The reaction liquor was discharged into iced water, and thereto was added

dropwise saturated aqueous sodium bicarbonate solution until there was no more effervescence, and the precipitated crystals were recovered by filtration. The obtained crude crystals were washed successively with ethanol and ether, and the title compound (250 mg, 99 %) was obtained.

Example 145

Synthesis of 5-benzoyl-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-5-(α-hydroxybenzyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one (4 g) prepared by a process in accordance with the literature (JOC, 24, 324 (1959)) was dissolved in anhydrous tetrahydrofuran (160 ml), and while cooling on an acetone-dry ice bath, n-butyllithium (hexane solution, 15 ml) was added dropwise and the mixture stirred for 30 minutes. Benzaldehyde (2 ml) dissolved in anhydrous tetrahydrofuran (80 ml) was gradually added dropwise while cooling on an acetone-dry ice bath, and the mixture was stirred for 90 minutes. Saturated ammonium chloride aqueous solution was added in a suitable quantity to the reaction liquor, and the liquid warmed to room temperature and thereafter extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: hexane : ethyl acetate = 5 : 1) and the title compound (852 mg, 14 %) was obtained.

mp.: 158.5-160.0°C

IR spectrum (KBr tablet) ν cm^{-1}: 3433, 1678, 1448, 1221, 748, 710.

NMR spectrum (DMSO-d_6) δ ppm: 8.41 (1H, d, J = 7.6 Hz), 8.23 (1H, d, J = 7.9 Hz), 7.79 (1H, d, J = 7.6 Hz), 7.59-7.22 (9H, m), 5.75 (1H, d, J = 4.3 Hz), 5.38 (1H, t, J = 4.3 Hz), 4.62 (1H, dd, J = 12.4, 8.6 Hz), 4.34 (1H, dd, J = 12.4, 6.4 Hz), 3.45-3.43 (1H, m).

Step 2

Synthesis of 5-benzoyl-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (83 mg, 11 %) was obtained from the compound obtained in Step 1 (700 mg) in accordance with Step 3 of Example 48.

Example 146

Synthesis of 5-(α-hydroxybenzyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

5-benzoyl-4H-pyrido [3,2,1-jk] carbazol-4-one (80 mg) obtained in Example 145 was dissolved in anhydrous tetrahydrofuran (80 ml) and under ice cooling, tri-t-butoxy lithium aluminium hydride (76 mg) was added and the mixture stirred for 30 minutes. Saturated ammonium chloride aqueous solution was added in a suitable quantity to the reaction liquor, and the liquid warmed to room temperature and thereafter extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (35 mg, 44 %) was obtained by reprecipitating the crude crystals of the residue from hexane and ethyl acetate.

Example 147

Synthesis of 5-anilino-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5-anilino-5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one

Copper (II) bromide (2.4 g) dissolved in ethyl acetate was heated under reflux under an argon atmosphere, and 5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one (2 g) prepared by a process in accordance with the literature (JOC, 24, 324 (1959)) and dissolved in chloroform (20 ml) was added dropwise and the mixture was heated under reflux under an argon atmosphere for 3 hours. After allowing to cool, the floating material was separated by filtration, and thereafter the filtrate was extracted with water and ethyl acetate.

The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The thereby obtained residue was added to aniline and warmed to 60°C on a warm bath and was stirred for 30 minutes. After allowing to cool, 1N hydrochloric acid was added and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: hexane : methylene chloride = 1 : 1) and the title compound (215 mg, 14 %) thereby obtained.

mp.: 149.7-152.0°C

IR spectrum (KBr tablet) ν cm^{-1}: 3342, 1693, 1601, 1500, 1319, 744
NMR spectrum (DMSO-d_6) δ ppm: 8.44 (1H, dd, J = 7.6, 1.0 Hz), 8.26 (1H, d, J = 7.6 Hz), 7.82 (1H, dd, J = 7.6, 1.0 Hz), 7.76 (1H, d, J = 8.3 Hz), 7.58-7.52 (1H, m), 7.38-7.27 (2H, m), 7.14-7.08 (2H, m), 6.83 (2H, d, J = 7.9 Hz), 6.61 (1H, t, J = 7.3 Hz), 6.16 (1H, d, J = 6.9 Hz), 5.09-4.92 (2H, m), 4.44-4.30 (1H, m).

Step 2

Synthesis of 5-anilino-4H-pyrido [3,2,1-jk] carbazole 4-one

The title compound (16 mg, 16 %) was obtained from the compound obtained in Step 1 (100 mg) in accordance with Step 3 of Example 48.

Example 148

Synthesis of 5-(N-methylanilino)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-5-(N-methylanilino)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (552 mg, 52 %) was obtained from 5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one (1 g) and N-methylaniline (1.06 ml) in accordance with Step 1 of Example 147.
mp.: 139.4-143.1°C
IR spectrum (KBr tablet) ν cm^{-1}: 1682, 1597, 1504, 1344, 1223, 748
NMR spectrum (DMSO-d_6) δ ppm: 8.45-8.42 (1H, m), 8.26 (1H, d, J = 7.9 Hz), 7.83 (1H, dd, J = 7.6, 0.7 Hz), 7.73 (1H, d, J = 8.3 Hz), 7.61-7.26 (3H, m), 7.19 (2H, dd, J = 8.6, 7.3 Hz), 6.99-6.89 (2H, m), 6.73-6.64 (1H, m), 5.74 (1H, dd, J = 12.5, 7.6 Hz), 4.95 (1H, dd, J = 11.9, 7.6 Hz), 4.69-4.53 (1H, m), 3.00 (3H, s).

Step 2

Synthesis of 5-(N-methylanilino)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (26 mg, 7 %) was obtained from the compound obtained in Step 1 (400 mg) in accordance with Step 3 of Example 48.

Example 149

Synthesis of 5-phenoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-5-phenoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (183 mg, 8.7 %) was obtained from 5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one (2 g) and phenol (0.72 g) in accordance with Step 1 of Example 147 .

mp.: 163.9-165.0°C

IR spectrum (KBr tablet) ν cm^{-1}: 1678, 1599, 1498, 1246, 1223, 744

NMR spectrum (DMSO-d_6) δ ppm: 8.47 (1H, dd, J =7.6, 0.7 Hz), 8.27 (1H, d, J = 7.6 Hz), 7.87-7.82 (1H, m), 7.75 (1H, d, J = 8.3 Hz), 7.63-7.50 (1H, m), 7.41-7.27 (4H, m), 7.11 (2H, d, J = 7.9 Hz), 7.00 (1H, t, J = 7.3 Hz), 5.78 (1H, dd, J = 8.3, 5.6 Hz), 5.04 (1H, dd, J = 12.5, 5.6 Hz), 4.71 (1H, dd, J = 12.5, 8.3 Hz).

Step 2

Synthesis of 5-phenoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (12 mg, 12 %) was obtained from the compound obtained in Step 1 (100 mg) in accordance with Step 3 of Example 48.

Example 150

Synthesis of 5-bromo-4H-pyrido [3,2,1-jk] carbazol-4-one

Copper (II) bromide (2.4 g) dissolved in ethyl acetate was heated under reflux under an argon atmosphere, and thereto was added dropwise 5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one (2 g) prepared by a process in accordance with the literature (JOC, 24, 324 (1959)) dissolved in chloroform (20 ml) and the mixture was heated under reflux under an argon atmosphere for 3 hours. After allowing to cool, the floating material was separated by filtration, and thereafter the filtrate was extracted with water and ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (18 mg, 18 %) was obtained from the thereby obtained residue (100 mg) by carrying out the procedures in accordance with Step 3 of Example 48.

Example 151

Synthesis of 5-(1-hydroxypropyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-5-(1-hydroxypropyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one (800 mg) prepared by a process in accordance with the literature (JOC, 24, 324 (1959)) was dissolved in anhydrous tetrahydrofuran (30 ml) and under cooling on an acetone-dry ice bath, n-butyllithium (hexane solution; 3 ml) was added dropwise, and the mixture was stirred for 30 minutes. Propionaldehyde (0.29 ml) dissolved in anhydrous tetrahydrofuran (15 ml) was gradually added dropwise under cooling on an acetone-dry ice bath, and the mixture was stirred for 90 minutes. Saturated ammonium chloride aqueous solution was added in a suitable quantity to the reaction liquor, and the liquid warmed to room temperature and thereafter extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: hexane : ethyl acetate = 4 : 1) and the title compound (450 mg, 45 %) thereby obtained as a diastereomer mixture.

mp.: 107.8°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 3466, 2958, 1655, 1597, 1483, 1219, 756

NMR spectrum (DMSO md5) δ ppm: 8.39 (1H, d, J =7.6 Hz), 8.23 (1H, d, J = 7.9 Hz), 7.84-7.65 (2H, m), 7.60-7.49 (1H, m), 7.38-7.21 (2H, m), 5.50-4.93 (1H, m), 4.72-4.50 (2H, m), 4.20-3.89 (1H, m), 3.29-2.99 (1H, m), 1.62-1.29 (2H, m), 0.99-0.79 (3H, m).

Step 2

Synthesis of 5-(1-hydroxypropyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (20 mg, 8 %) was obtained from the compound obtained in Step 1 (250 mg) in accordance with Step 3 of Example 48

Example 154

Synthesis of 2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 1, Step 2 and Step 3 of Example 1, the title compound was obtained from the 3-bromo carbazole prepared using a process in accordance with the literature (Industrial Chemistry Journal 70, 63 (1967)).

mp.: 127.7-129.6°C

IR spectrum (KBr tablet) ν cm^{-1}: 1653, 1479, 1460, 1392, 1140, 746

NMR spectrum (DMSO-d_6) δ ppm: 8.22 (1H, d, J =7.3 Hz), 8.07 (1H, d, J = 2.4 Hz), 7.64 (1H, d, J = 8.3 Hz), 7.52 (1H, dd, J = 8.3, 7.3 Hz), 7.34 (1H, d, J = 2.4 Hz), 7.28-7.19 (1H, m), 4.54 (2H, t, J =7.0 Hz), 3.89 (3H, s), 3.13 (2H, t, J = 7.0 Hz).

Step 2

Synthesis of 2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Step 4 of Example 1, the title compound (1.64 g, 61 %) was obtained from the compound obtained in Step 1 (2 g).

Example 161

Synthesis of 2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Step 1 of Example 1, 3-methoxy carbazole was synthesized from 3-bromo carbazole prepared using a process in accordance with the literature (Industrial Chemistry Journal, 70, 63 (1967)), and the title compound was obtained according to the procedures of Step 1 and Step 2 of Example 48.

mp.: 164.8-168.2°C.

IR spectrum (KBr tablet) ν cm^{-1}: 1653, 1460, 1201, 1092, 1032, 746

NMR spectrum (DMSO-d_6) δ ppm: 8.22 (1H, d, J = 7.8 Hz), 8.07 (1H, d, J = 2.4 Hz), 7.64 (1H, d, J = 8.3 Hz), 7.58-7.47 (1H, m), 7.34 (1H, d, J = 2.4 Hz), 7.33-7.23 (1H, m), 4.78 (1H, dd, J = 11.8, 6.7 Hz), 4.17-4.02 (1H, m), 3.89 (3H, s), 3.33-3.31 (1H, m), 1.30 (3H, d, J = 6.7 Hz).

Step 2

Synthesis of 2-methoxy-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Step 3 of Example 48, the title compound (1.45 g, 73 %) was obtained from the compound obtained in Step 1 (2 g).

Example 171

Synthesis of 2-chloro-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 6-chloro-1,2,3,4-tetrahydrocarbazole

To 4-chlorophenyl hydrazine hydrochloride (25 g) suspended in acetic acid (120 ml) was added cyclohexanone (14.5 ml) and the mixture heated under reflux for two hours. The mixture was cooled to 0°C and the precipitated crystals were recovered by filtration and washed with water and ethanol. The title compound (12.4 g, 43 %) was obtained by recrystallizing the crude product from methanol.

mp.: 146.3-146.4°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3406, 2939, 1470, 1439, 1057, 800, 592.

NMR spectrum (DMSO-d_6) δ ppm: 10.84 (1H, s), 7.33 (1H, d, J = 2.1 Hz), 7.21 (1H, d, J = 8.5 Hz), 6.96 (1H, dd, J = 8.5, 2.1 Hz), 2.73-2.57 (4H, m), 1.84-1.76 (4H, m).

Step 2

Synthesis of 6-chloro-1,2,3,4-tetrahydrocarbazole-N-β-propionic acid

The compound obtained in Step 1 (10 g) was suspended in 50 ml acetone and cooled on an ice bath, and thereafter, thereto were added dropwise methyl acrylate (8.8 ml) and then Triton B (2 ml). After stirring for 1 hour, the solvent was eliminated by distillation under reduced pressure. The thereby obtained residue was suspended in 20 ml methanol, and sodium hydroxide (4.3 g) dissolved in water (50 ml) was added dropwise at room temperature and the mixture was heated under reflux for 20 minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter, water and ether were added and liquid separation was carried out. The aqueous layer was made acidic by the addition of 4N hydrochloric acid, thereafter the thereby formed precipitate was dissolved in ethyl acetate, washed successively with water and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. Crude crystals of the residue were washed with hexane and ether, and the title compound (10.1 g, 75 %) was obtained.

mp.: 158.1-159.1°C

IR spectrum (KBr tablet) ν cm^{-1}: 2935, 1711, 1471, 1446, 1290, 957, 797.

NMR spectrum (DMSO-d_6) δ ppm: 12.4 (1H, s), 7.43-7.37 (2H, m), 7.03 (1H, dd, J = 8.9, 2.0 Hz), 4.27 (2H, t, J = 5.4Hz), 2.73 (2H, t, J =5.4 Hz), 2.64-2.56 (4H, m), 1.86-1.75 (4H, m).

Step 3

Synthesis of 2-chloro-8,9,10,11-tetrahydro-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 2 (10 g) was suspended in anhydrous toluene (200 ml) and diphosphorous pentoxide (51 g) was added and the mixture was heated under reflux under an argon atmosphere for 3 hours. The reaction liquor was discharged into water after allowing to cool, the insolubles were separated by filtration using celite, and thereafter the filtrate was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (1.47 g, 16 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: ethyl acetate).

mp.: 255.7-258.2°C.

IR spectrum (KBr tablet) ν cm^{-1}: 2929, 1614, 1595, 1554, 1489, 1277, 1207, 824

NMR spectrum (DMSO-d_6) δ ppm: 8.33 (1H, d, J = 7.8 Hz), 7.93 (1H, d, J = 1.7 Hz), 7.75 (1H, d, J = 1.7 Hz), 6.21 (1H, d, J = 7.8 Hz), 2.93-2.80 (2H, m), 2.72-2.61 (2H, m), 1.93-1.80 (4H, m).

Step 4

Synthesis of 2-chloro-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 3 (0.8 g) was dissolved in anhydrous dioxane (20 ml) and DDQ (1.48 g) was added at room temperature, and thereafter the mixture was heated under reflux for 6 hours under an argon atmosphere. After allowing to cool, the reaction liquor was added to 1N sodium hydroxide and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (320 mg, 41 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: methylene chloride : ethyl acetate = 2 : 1).

Example 172

Synthesis of 2-chloro-5-methyl-4H-pyrido (3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 2-chloro-5,6-dihydro-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 1 and Step 2 of Example 48, the title compound was obtained from the 3-chloro carbazole prepared using a process in accordance with the literature (Rec Trav Chim, 73, 197 (1954)).

mp.: 155.2-159.2°C.

IR spectrum (KBr tablet) ν cm^{-1}: 2931, 1680, 1446, 1136, 746

NMR spectrum (DMSO-d_6) δ ppm: 8.51 (1H, d, J = 2.0 Hz), 8.31-8.22 (1H, m), 7.73-7.64 (2H, m), 7.58 (1H, t, J = 7.1 Hz), 7.31 (1H, t, J = 7.1 Hz), 4.85 (1H, dd, J = 12.2, 6.6 Hz), 4.21-4.08 (1H, m), 3.42-3.26 (1H, m), 1.31 (3H, d, J = 6.9 Hz).

Step 2

Synthesis of 2-chloro-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 4 of Example 171, the title compound (9 mg, 20 %) was obtained from the compound obtained in Step 1 (45 mg).

Example 173

Synthesis of 2-cyano-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 6-bromo-1,2,3,4-tetrahydrocarbazole-N-β-propionic acid

In accordance with the procedures of Step 1 and Step 2 of Example 171, the title compound was synthesized from the 4-bromo phenylhydrazine hydrochloride and methyl acrylate.

mp.: 167.0°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 2935, 1711, 1470, 1288, 1263, 793

NMR spectrum (DMSO-d_6) δ ppm: 12.38 (1H, bs), 7.51 (1H, d, J = 2.0 Hz), 7.38 (1H, d, J = 8.5 Hz), 7.15 (1H, dd, J = 8.5, 2.0 Hz), 4.27 (2H, t, J = 7.1 Hz), 2.76-2.64 (2H, m), 2.62-2.51 (4H, m), 1.85-1.75 (4H, m).

Step 2

Synthesis of 2-bromo-5,6,8,9,10,11-hexahydro-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 1 (170 g) was suspended in anhydrous toluene (3 l), and diphosphorous pentoxide (750 g) was added and the mixture was heated under reflux under an argon atmosphere for five hours. After allowing to cool, the reaction liquor was discharged into water, the insolubles were separated by filtration using celite, and thereafter, the filtrate was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (30 g, 19 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: ethyl acetate).

mp.: 153.3°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 2929, 1676, 1489, 1417, 1367, 1186, 1126

NMR spectrum (DMSO-d_6) δ ppm: 7.84 (1H, d, J = 1.5 Hz), 7.43 (1H, d, J = 1.5 Hz), 4.31 (2H, t, J = 7.0 Hz), 3.02 (2H, t, J = 7.0 Hz), 2.81-2.57 (4H, m), 1.99-1.77 (4H, m).

Step 3

Synthesis of 2-cyano-5,6,8,9,10,11-hexahydro-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 2 (20 g) was suspended in anhydrous dimethylformamide (30 ml), and copper cyanide (25 g) was added, and the mixture was stirred under an argon atmosphere while heating at 120-140°C on an oil bath for five hours. After allowing to cool, the reaction liquor was added to ethylene diamine aqueous solution (400 ml) and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (12 g, 73 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: ethyl acetate).

mp.: 222.5°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 2929, 2214, 1691, 1502, 887.

NMR spectrum (DMSO-d_6) δ ppm: 8.17 (1H, s), 7.68 (1H, s), 4.38 (2H, t, J = 6.8 Hz), 3.06 (2H, t, J = 6.8 Hz), 2.83-2.62 (4H, m), 1.95-1.71 (4H, m).

Step 4

Synthesis of 2-cyano-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 3 (2 g) was dissolved in anhydrous dioxane (250 ml), and DDQ

(6.53 g) was added at room temperature, and thereafter the mixture was heated under reflux for 12 hours under an argon atmosphere. After allowing to cool, the reaction liquor was added to 1N sodium hydroxide and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (1 g, 51 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: 2 % ethyl acetate-containing methylene chloride).

Example 174

Synthesis of 2-carbamoyl-4H-pyrido [3,2,1-jk] carbazol-4-one

To a 88 ml ethylene glycol mono ethyl ether suspension of 2-cyano-4H-pyrido [3,2,1-jk] carbazol-4-one (880 mg) obtained in Example 173 was added 1N sodium hydroxide aqueous solution (5.3 ml) and thereafter the mixture was heated under reflux under an argon atmosphere for four hours. After allowing to cool, the reaction liquor was added to 2N sodium hydroxide aqueous solution and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (180 mg, 20 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: ethyl acetate).

Example 175

Synthesis of 2-carboxy-4H-pyrido [3,2,1-jk] carbazol-4-one

To a concentrated nitric acid (13 ml) suspension of 2-carbamoyl-4H-pyrido [3,2,1-jk] carbazol-4-one (350 mg) obtained in Example 174 was added sodium nitrite (1.84 g) under ice cooling, and the mixture stirred at room temperature for 12 hours. Water was added to the reaction liquor, the precipitated crystals were recovered by filtration, and the title compound (300 mg, 85 %) was obtained by washing successively with methanol and ether.

Example 176

Synthesis of 2-methoxycarbonyl-4H-pyrido [3,2,1-jk] carbazol-4-one

2-carboxy-4H-pyrido [3,2,1-jk] carbazol-4-one (500 mg) obtained in Example 175 was suspended in 100 ml tetrahydrofuran, and methanol (several drops) was added, and thereafter, trimethylsilyldiazomethane (2M hexane solution, 1 ml) was added dropwise at room temperature and

the mixture stirred for 90 minutes. The solvent was eliminated by distillation under reduced pressure, and the title compound (250 mg, 48 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: ethyl acetate).

Example 177

Synthesis of 2-hydroxymethyl-4H-pyrido [3,2,1-jk] carbazol-4-one

2-methoxycarbonyl-4H-pyrido [3,2,1-jk] carbazol-4-one (300 mg) obtained in Example 176 was suspended in anhydrous methylene chloride (100 ml), and under cooling on an acetone-dry ice bath, diisobutyl aluminium hydride (1M methylene chloride solution; 4.3 ml) was added dropwise, and stirring was carried out at room temperature for 1 hour. Methanol and water were added to the reaction liquor, and the formed floating substances were separated by filtration, and the filtrate was concentrated down by distillation under reduced pressure. The title compound (70 mg, 26 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: ethyl acetate).

Example 178

Synthesis of 2-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 2-bromo-5-(3-pyridylmethyl)-8,9,10,11-tetrahydrocarbazol-4-one

In accordance with the procedures of Step 4 of Example 1, the title compound (5.52 g, 86 %) was obtained from 2-bromo-5,6,8,9,10,11-hexahydro-4H-pyrido [3,2,1-jk] carbazol-4-one (5 g) obtained in Step 2 of Example 173 and pyridine-3-aldehyde (5 g).

mp.: 326.0°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 2941, 1612, 1589, 1572, 1493, 1294

NMR spectrum ($CDCl_3$) δ ppm: 8.58 (1H, d, J = 1.5 Hz), 8.47 (1H, dd, J, 4.9, 1.5 Hz), 8.22 (1H, d, J = 1.5 Hz), 7.84 (1H, d, J = 1.5 Hz), 7.75-7.66 (1H, m), 7.63 (1H, s), 7.22 (1H, dd, J = 8.3, 4.9 Hz), 3.92 (2H, s), 2.82-2.68 (4H, m), 2.05-1.89 (4H, m).

Step 2

Synthesis of 2-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 4 of Example 171, the title compound (12 mg, 1 %) was obtained from the compound obtained in Step 1 (3 g).

Example 179

Synthesis of 2-amino-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

2-bromo-5-(3-pyridyl methyl)-4H-pyrido [3,2,1-jk] carbazol-4-one obtained in Example 178 (555 mg), copper (20 mg) and copper iodide (10 mg) were suspended in ammonia water (28 %, 30 ml) in a pressure resistant microcylinder, and the suspension was warmed to 180-190°C on an oil bath and the mixture stirred for 8 hours. The reaction liquor was returned to normal pressure by allowing to cool, and thereafter extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: ethyl acetate) and thereafter the title compound (120 mg, 26 %) was obtained by recrystallizing the crude purified material from ethanol.

Example 184

Synthesis of 10-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 10-bromo-5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 2 and Step 3 of Example 1, the title compound was obtained from the 3-bromo carbazole prepared using a process in accordance with the literature (Industrial Chemistry Journal, 70, 63 (1967)).

mp.: 134.3 (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 1626, 1597, 1487, 1219. 797, 746.

NMR spectrum (DMSO-d_6) δ ppm: 8.55-8.41 (2H, m), 7.81 (1H, dd, J = 7.8, 1.0 Hz) 7.73-7.62 (2H, m), 7.33 (1H, t, J = 7.6 Hz), 4.60 (2H, t, J =7.1 Hz), 3.14 (2H, t, J = 7.1 Hz).

Step 2

Synthesis of 10-bromo-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 4 of Example 1, the title compound (4.65 g, 90 %) was obtained from the compound obtained in Step 1 (4 g).

Example 190

Synthesis of 10-chloro-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 10-chloro-5,6-dihydro-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 1 and Step 2 of Example 48, the title compound was obtained from 3-chloro carbazole prepared using a process in accordance with the literature (Rec Trav Chim, 73, 197 (1954)).

mp.: 146.2 - 151.7°C

IR spectrum (KBr tablet) ν cm^{-1}: 1682, 1597, 1485, 1335, 1228, 1215, 746

NMR spectrum (DMSO-d_6) δ ppm: 8.45 (1H, d, J = 7.6 Hz), 8.37 (1H, d, J = 2.1 Hz), 7.82 (1H, d, J = 7.6 Hz), 7.71 (1H, d, J = 8.8 Hz), 7.56 (1H, dd, J = 8.8, 2.1 Hz), 7.33 (1H, t, J = 7.6 Hz), 4.84 (1H, dd, J = 12.2, 6.7 Hz), 4.22-4.08 (1H, m), 3.46-3.24 (1H, m), 1.30 (3H, d, J = 6.7 Hz).

Step 2

Synthesis of 10-chloro-5-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (1 g, 67 %) was obtained from the compound obtained in Step 1 (1.5 g) in accordance with Step 3 of Example 48.

Example 193

Synthesis of 10-chloro-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 10-chloro-5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 2 and Step 3 of Example 1, the title compound was obtained from 3-chloro carbazole prepared using a process in accordance with the literature (Rec Trav Chim, 73, 197 (1954)).

mp.: 144.3-147.9°C

IR spectrum (KBr tablet) ν cm^{-1}: 1682, 1489, 1346, 1333, 1219, 798

NMR spectrum (DMSO-d_6) δ ppm: 8.52-8.38 (2H, m), 7.81 (1H, dd, J = 7.8, 1.0 Hz), 7.73 (1H, d, J = 8.8 Hz), 7.57 (1H, dd, J = 8.8, 2.4 Hz), 7.33 (1H, t, J = 7.1 Hz), 4.61 (2H, t, J = 7.1 Hz), 3.14 (2H, t, J = 7.1 Hz).

Step 2

Synthesis of 10-chloro-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Example 58, the title compound (1 g, 34.0 %) was obtained from the compound obtained in Step 1 (3 g).

Example 194

Synthesis of 10-acetyl-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 10-acetyl-5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 2 and Step 3 of Example 1, the title compound was obtained from 3-acetyl carbazole prepared using a process in accordance with the literature (Rec Trav Chim, 66, 533 (1947)).

mp.: 192.1-196.2°C

IR spectrum (KBr tablet) ν cm^{-1}: 1678, 1657, 1485, 1213, 804

NMR spectrum (DMSO-d_6) δ ppm: 8.96 (1H, s), 8.55 (1H, d, J = 7.3 Hz), 8.17 (1H, d, J = 8.8 Hz), 7.83 (1H, d, J = 7.8 Hz), 7.77 (1H, d, J = 8.8 Hz), 7.43-7.34 (1H, m), 4.67 (2H, t, J = 7.1 Hz), 3.16 (2H, t, J = 7.1 Hz), 2.70 (3H, s).

Step 2

Synthesis of 10-acetyl-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Step 4 of Example 1, the title compound (580 mg, 43 %) was obtained from the compound obtained in Step 1 (1 g).

Example 195

Synthesis of 10-carboxy-5-(3-pyridylmethyl)-4H-pyrido-[3,2,1-jk] carbazol-4-one

Sodium hydroxide (300 mg) was dissolved in water (15 ml), bromine (0.1 ml) was added dropwise while cooling on an ice bath and the mixture was diluted with dioxane (14 ml). This solution prepared beforehand was added dropwise while ice cooling to 10-acetyl-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (190 mg) obtained in Example 194 dissolved in 30 ml dioxane. After stirring for five minutes, sodium sulfite (70 mg) dissolved in water (10 ml) was added and liquid separation was carried out using ether. The pH was adjusted to pH7 by the addition of 1N hydrochloric acid to the aqueous layer, and thereafter the precipitated crystals were recovered by filtration, washed

successively with methanol and acetone and the title compound (67 mg, 35 %) thereby obtained.

Example 198

Synthesis of 5-benzyl-10-(4-morpholino acetyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Phenyl trimethylammonium tribromide (170 mg) was added to the anhydrous tetrahydrofuran (10 ml) suspension of 10-acetyl-5-benzyl-4H-pyrido [3,2,1-jk] carbazol-4-one (100 mg) obtained in Example 196 and the mixture was heated under reflux under an argon atmosphere for 3 hours. After allowing to cool, extraction was carried out with water and ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The thereby obtained residue was suspended in ethanol (10 ml), morpholine (30 μl) and sodium bicarbonate (30 mg) were added and the mixture heated under reflux under an argon atmosphere for 1 hour. After allowing to cool, extraction was carried out with water and ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was refined by silica gel flash column chromatography (eluting solvent: methylene chloride : methanol = 20 : 1) and the title compound (12 mg, 9.6 %) was obtained.

Example 199

Synthesis of 5-benzyl-10-(1-hydroxyethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-acetyl-5-benzyl-4H-pyrido [3,2,1-jk] carbazol-4-one (150 mg) obtained in Example 196 was suspended in 15 ml methanol, and 1N sodium hydroxide (one drop) was added, and after cooling on an ice bath, sodium borohydride (161 mg) was gradually added and the mixture stirred at room temperature for 1 hour. Saturated sodium bicarbonate was added in a small amount to the reaction liquor and extraction with ethyl acetate carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. Crude crystals of the residue were washed with a mixed solvent of ether and hexane, and the title compound (126 mg, 83 %) was obtained.

Example 203

Synthesis of 1-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-1-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 2 and Step 3 of Example 1, the title compound was obtained from the 4-methoxy carbazole prepared using a process in accordance with the literature (J. Heterocyclic Chem, 25, 907 (1988)).

mp.: 133.5-136.7°C.

IR spectrum (KBr tablet) ν cm^{-1}: 1670, 1601, 1363, 1259, 746

NMR spectrum (DMSO-d_6) δ ppm: 8.14 (1H, d, J =7.9 Hz), 7.81 (1H, d, J = 8.3 Hz), 7.65 (1H, d, J = 8.3 Hz), 7.52-7.46 (1H, m), 7.28 (1H, t, J =7.9 Hz), 6.91 (1H, d, J = 8.3 Hz), 4.55 (2H, t, J = 7.0 Hz), 4.12 (3H, s), 3.07 (2H, t, J = 7.0 Hz).

Step 2

Synthesis of 1-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 4 of Example 1, the title compound (1.2 g, 89 %) was obtained from the compound obtained in Step 1 (1 g).

Example 210

Synthesis of 3-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-3-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

According to the procedures of Steps 1, 2 and 3 of Example 1 and Step 4 of Example 101, the title compound was obtained from commercial 2-hydroxycarbazole.

mp.: 148.9-150.7°C

IR spectrum (KBr tablet) ν cm^{-1}: 1674, 1601, 1585, 1250, 1174, 1122, 1099, 754

NMR spectrum (DMSO-d_6) δ ppm: 8.30 (1H, d, J = 8.7 Hz), 8.10 (1H, dd, J = 7.6, 1.0 Hz), 7.58 (1H, d, J = 7.9 Hz), 7.50-7.39 (1H, m), 7.24 (1H, t, d, J = 7.9, 1.0 Hz), 6.94 (1H, d, J = 8.7 Hz), 4.49 (2H, t, J = 7.1 Hz), 3.91 (3H, s), 3.00 (2H, t, J = 7.1 Hz).

Step 2

Synthesis of 3-methoxy-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (1.61 g, 79 %) was obtained from the compound obtained in Step 1 (1.5 g) in accordance with Step 4 of Example 1.

Example 216

Synthesis of 8-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-8-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 2 and Step 3 of Example 1, the title compound was obtained from 1-methoxy carbazole prepared using a process in accordance with the literature (JCS Perkin I, 235 (1988)).

mp.: 177.5-180.3°C.

IR spectrum (KBr tablet) ν cm^{-1}: 1682, 1576, 1441, 1292, 1257, 770

NMR spectrum (DMSO-d_6) δ ppm: 8.37 (1H, dd, J = 7.6, 1.0 Hz), 7.87-7.76 (2H, m), 7.30 (1H, t, J = 7.6 Hz), 7.23 (1H, t, J = 7.9 Hz), 7.12 (1H, dd, J = 7.9, 1.0 Hz), 4.85 (2H, t, J = 7.0 Hz), 3.99 (3H, s), 3.13 (2H, d, J = 7.0 Hz).

Step 2

Synthesis of 8-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (1.54 g, 76 %) was obtained from the compound obtained in Step 1 (1.5 g) in accordance with Step 4 of Example 1.

Example 224

Synthesis of 9-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-9-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 4 of Example 101 and Step 2 and Step 3 of Example 1, the title compound was obtained from commercial 2-hydroxycarbazole.

mp.: 115.4-117.5°C

IR spectrum (KBr tablet) ν cm^{-1}: 1680, 1630, 1475, 1356, 1223, 1082, 743

NMR spectrum (DMSO-d_6) δ ppm: 8.27 (1H, d, J = 7.6 Hz), 8.09 (1H, d, J = 8.7 Hz), 7.68 (1H, d, J =

7.6 Hz), 7.28-7.22 (2H, m), 6.89 (1H, dd, J = 8.7, 2.1 Hz), 4.56 (2H, t, J = 7.0 Hz), 3.90 (3H, s), 3.12 (2H, t, J = 7.0 Hz).

Step 2

Synthesis of 9-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (1.52 g, 74 %) was obtained from the compound obtained in Step 1 (1.52 g) in accordance with Step 4 of Example 1.

Example 232

Synthesis of 11-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-11-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with the procedures of Step 2 and Step 3 of Example 1, the title compound was obtained from 4-methoxy carbazole prepared using a process in accordance with the literature (J. Heterocyclic Chem, 25, 907 (1988)).

mp.: 177.8-180.7°C

IR spectrum (KBr tablet) ν cm^{-1}: 1670, 1489, 1458, 1346, 1273, 746

NMR spectrum ($DMSO-d_6$) δ ppm: 8.31 (1H, dd, J = 6.6, 1.0 Hz), 7.74 (1H, dd, J = 7.6, 1.0 Hz), 7.55-7.46 (1H, m), 7.34-7.23 (2H, m), 6.87 (1H, d, J = 8.3 Hz), 4.57 (2H, t, J = 7.1 Hz), 4.05 (3H, s), 3.13 (2H, t, J = 7.1 Hz).

Step 2

Synthesis of 11-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (230 mg, 78 %) was obtained from the compound obtained in Step 1 (220 mg) in accordance with Step 4 of Example 1.

Example 235

Synthesis of 10-fluoro-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 6-fluoro-1,2,3,4-tetrahydrocarbazole

The title compound (126 g, 83 %) was obtained from the commercial 4-fluorophenyl hydrazine (130 g) in accordance with Step 1 of Example 171.

mp.: 107.6°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 3408, 2931, 1583, 1483, 1446, 795

NMR spectrum ($CDCl_3$) δ ppm: 7.66 (1H, bs), 7.17 (1H, dd, J = 8.9, 4.3 Hz), 7.09 (1H, dd, J = 9.6, 2.6 Hz), 6.88-6.80 (1H, m), 2.74-2.64 (4H, m), 1.96-1.82 (4H, m).

Step 2

Synthesis of 3-fluoro carbazole

The compound obtained in Step 1 (1 g) was dissolved in xylene (6 ml) and chloranil (1.3 g) was added and the mixture was heated under reflux under an argon atmosphere for 3 hours. After allowing to cool, the reaction liquor was decanted, the insolubles were separated by filtration and the filtrate was concentrated under reduced pressure. The title compound (232 mg, 24 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: hexane : ethyl acetate = 15 : 1).

mp.: 203.2°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 3419, 1585, 1497, 1169, 746

NMR spectrum (DMSO-d_6) δ ppm: 11.29 (1H, bs), 8.13 (1H, d, J = 7.8 Hz), 7.95 (1H, dd, J = 9.5, 2.7 Hz), 7.53-7.37 (3H, m), 7.30-7.11 (2H, m).

Step 3

Synthesis of 3-bromo-6-fluoro carbazole

The compound obtained in Step 2 (13.5 g) was dissolved in 200 ml dimethylformamide, and under ice cooling, N-bromo succinimide (14.2 g) dissolved in dimethylformamide (136 ml) was added dropwise and the mixture stirred for 15 minutes. The reaction liquor was discharged into iced water and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (16.8 g, 87 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: hexane : ethyl acetate = 8 : 1).

mp.: 158.0°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 3410, 1489, 1443, 1161, 810, 571.

NMR spectrum (DMSO-d_6) δ ppm: 11.48 (1H, s), 8.40 (1H, d, J = 2.0 Hz), 8.03 (1H, dd, J = 9.5, 2.7 Hz), 7.55-7.45 (3H, m), 7.32-7.24 (1H, m).

Step 4

Synthesis of 5,6-dihydro-10-fluoro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound was obtained from the compound obtained in Step 3 in accordance with Step 1, Step 2 and Step 3 of Example 1.

mp.: 166.8-169.4°C

IR spectrum (KBr tablet) ν cm^{-1}: 1672, 1483, 1290, 1190, 1124, 854, 783.

NMR spectrum (DMSO-d_6) δ ppm: 8.09 (1H, d, J = 2.4 Hz), 8.07 (1H, d, J = 2.4 Hz), 7.66 (1H, dd, J = 8.8, 4.4 Hz), 7.42-7.35 (2H, m), 4.54 (2H, t, J = 7.1 Hz), 3.88 (3H, s), 3.13 (2H, t, J = 7.1 Hz).

Step 5

Synthesis of 10-fluoro-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (2.28 g, 86 %) was obtained from the compound obtained in Step 4 (2 g) in accordance with Step 4 of Example 1.

Example 238

Synthesis of 2-butyryloxy-10-fluoro-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-fluoro-2-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (150 mg) obtained in Example 236 was suspended in 12 ml pyridine, and n-butyryl chloride (74 μl) was added dropwise under ice cooling. After stirring for 50 minutes, the solvent was eliminated by distillation under reduced pressure. The residue was washed with ether and the title compound (126 mg, 70 %) thereby obtained.

Example 243

Synthesis of 10-chloro-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 3-methoxy carbazole

In accordance with the procedures of Step 1 of Example 1, the title compound (76 g, 82 %) was obtained from 3-bromo carbazole (116 g) prepared using a process in accordance with the literature (Industrial Chemistry Journal, 70, 63 (1967)).

mp.: 153.2-154.3°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3406, 1497, 1460, 1171, 1034, 820, 748.

NMR spectrum (DMSO-d_6) δ ppm: 11.03 (1H, s), 8.09 (1H, d, J = 7.8 Hz), 7.67 (1H, d, J = 2.3 Hz),

7.45-7.31 (3H, m), 7.13-7.08 (1H, m), 7.02 (1H, dd, J = 8.8, 2.3 Hz), 3.84 (3H, s).

Step 2

Synthesis of 3-chloro-6-methoxy carbazole

The title compound (6.4 g, 17 %) was obtained from the compound obtained in Step 1 (33 g) and N-chlorosuccinimide (23.5 g) in accordance with Step 3 of Example 235.

mp.: 152.7-154.9°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3415, 1491, 1462, 1223, 1205, 1169, 814

NMR spectrum (DMSO-d_6) δ ppm: 11.21 (1H, s), 8.21 (1H, d, J = 2.0 Hz), 7.75 (1H, d, J = 2.4 Hz), 7.47-7.32 (3H, m), 7.05 (1H, dd, J = 8.8, 2.4 Hz), 3.84 (3H, s).

Step 3

Synthesis of 10-chloro-5,6-dihydro-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound was obtained from the compound obtained in Step 2 in accordance with Step 2 and Step 3 of Example 1.

mp.: 162.2-168.2°C

IR spectrum (KBr tablet) ν cm^{-1}: 1672, 1495, 1479, 1288, 1200, 798

NMR spectrum (DMSO-d_6) δ ppm: 8.36 (1H, d, J = 2.4 Hz), 8.14 (1H, d, J = 2.3 Hz), 7.68 (1H, d, J = 8.6 Hz), 7.54 (1H, dd, J = 8.6, 2.3 Hz), 7.37 (1H, d, J = 2.4 Hz), 4.55 (2H, t, J = 7.0 Hz), 3.88 (3H, s), 3.13 (2H, t, J = 7.0 Hz).

Step 4

Synthesis of 10-chloro-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (850 mg, 69 %) was obtained from the compound obtained in Step 3 (950 mg) in accordance with Step 4 of Example 1.

Example 248

Synthesis of 10-ethyl-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 4-acetyl-4'-methoxy diphenylamine

To 11 ml dibutyl ether were added p-aminoacetophenone (1 g), 4-iodo anisole (3.46 g), potassium carbonate (2.04 g) and copper (25 mg), and the mixture was heated under reflux for 8 hours under an

argon atmosphere. After allowing to cool, the insolubles were separated by filtration, and thereafter the filtrate was concentrated down by distillation under reduced pressure. The title compound (368 mg, 21 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: hexane : ethyl acetate = 3 : 1).

mp.: 116.5-120.9°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3307, 1649, 1587, 1508, 1279, 1244, 833

NMR spectrum (*DMSO-d_6) δ ppm: 8.58 (1H, s), 7.77 (2H, d, J = 8.8 Hz), 7.13 (2H, d, J = 8.8 Hz), 6.94 (2H, d, J = 8.8 Hz), 6.88 (2H, d, J = 8.8 Hz), 3.75 (3H, s), 2.43 (3H, s).

Step 2

Synthesis of 3-acetyl-6-methoxy carbazole

The compound obtained in Step 1 (100 mg) was dissolved in acetic acid (5 ml), and palladium acetate (186 mg) was added and the mixture heated under reflux for ten minutes under an argon atmosphere. The insolubles were separated by filtration after allowing to cool, and extraction was carried out with water and ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (34 mg, 34 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: hexane : ethyl acetate = 3 : 1).

mp.: 203.6-207.7°C

IR spectrum (KBr tablet) ν cm^{-1}: 1659, 1630, 1495, 1269, 1219, 1028

NMR spectrum (*DMSO-d_6) δ ppm: 11.52 (1H, s), 8.86 (1H, d, J = 1.5 Hz), 7.99 (1H, dd, J = 8.6, 1.5 Hz), 7.87 (1H, d, J = 2.4 Hz), 7.50 (1H, d, J = 8.6 Hz), 7.44 (1H, d, J = 8.7 Hz), 7.07 (1H, dd, J = 8.7, 2.4 Hz), 3.87 (3H, s), 2.67 (3H, s).

Step 3

Synthesis of 3-ethyl-6-methoxy carbazole

The compound obtained in Step 2 (6.24 g) was suspended in acetic acid (460 ml), and thereto were added 10 % palladium carbon (4.6 g) and sodium acetate (10.3 g), and the mixture was heated under reflux under a hydrogen atmosphere for 90 minutes. After allowing to cool, the insolubles were separated by filtration, and the filtrate was discharged into water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (6.24 g, 66 %) was obtained by refining the residue by silica gel flash

column chromatography (eluting solvent: hexane : ethyl acetate = 7 : 1).

mp.: 87.5-91.2°C

IR spectrum (KBr tablet) ν cm^{-1}: 3404, 2958, 1497, 1468, 1209, 1149, 1032

NMR spectrum (*DMSO-d_6) δ ppm: 10.88 (1H, bs), 7.92-7.88 (1H, m), 7.64 (1H, d, J = 2.5 Hz), 7.38-7.33 (2H, m), 7.20 (1H, dd, J = 8.5, 1.5 Hz), 6.98 (1H, dd, J = 8.5, 2.5 Hz), 3.83 (3H, s), 2.75 (2H, q, J = 7.5 Hz), 1.27 (3H, t, J = 7.5 Hz).

Step 4

Synthesis of 5,6-dihydro-10-ethyl-2-methoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound was obtained from the compound obtained by Step 3 in accordance with Step 2 and Step 3 of Example 1.

mp.: 109.3-110.3°C.

IR spectrum (KBr tablet) ν cm^{-1}: 2964, 1676, 1500, 1485, 1300, 1227, 1082.

NMR spectrum (*DMSO-d_6) δ ppm: 8.05-8.03 (2H, m), 7.54 (1H, d, J = 8.3 Hz), 7.38 (1H, dd, J = 8.3, 1.7 Hz), 7.30 (1H, d, J = 2.2 Hz), 4.50 (2H, t, J = 7.1 Hz), 3.88 (3H, s), 3.11 (2H, t, J = 7.1 Hz), 2.78 (2H, q, J = 7.6 Hz), 1.28 (3H, t, J = 7.6 Hz).

Step 5

Synthesis of 10-ethyl-2-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (507 mg, 96 %) was obtained from the compound obtained in Step 4 (400 mg) in accordance with Step 4 of Example 1.

Example 253

Synthesis of 2-hydroxy-10-methoxy-5-(3-pyridylmethyl) 4H-pyrido [3,2,1-jk] carbazol-4-one

2-benzyloxy-10-methoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (470 mg) obtained in Example 252 was dissolved in acetic acid, and sodium acetate (259 mg) and palladium carbon (116 mg) were added and the mixture heated under reflux under a hydrogen atmosphere for 3 hours. The reaction liquor was filtered, and the filtrate was concentrated down by distillation under reduced pressure. Sodium bicarbonate aqueous solution was added to the residue until there was no more effervescence and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and the solvent was eliminated by distillation under reduced pressure. The title compound (257 mg, 62 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: methylene

chloride : methanol = 20 : 1).

Example 257

Synthesis of 2,10-dimethoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk) carbazol-4-one

Step 1

Synthesis of 5,6-dihydro-2,10-dimethoxy-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Step 1, Step 2 and Step 3 of Example 1, the title compound was obtained from the commercial 3,6-dibromo carbazole.

mp.: 136.7-140.4°C.

IR spectrum (KBr tablet) ν cm^{-1}: 1670, 1485, 1458, 1215, 1130, 1076, 771

NMR spectrum (DMSO-d_6) δ ppm: 8.07 (1H, d, J = 2.4 Hz), 7.82 (1H, d, J = 2.4 Hz), 7.56 (1H, d, J = 8.7 Hz), 7.31 (1H, d, J = 2.4 Hz), 7.15 (1H, dd, J = 8.7, 2.4 Hz), 4.48 (2H, t, J = 7.1 Hz), 3.88 (3H, s), 3.86 (3H, s), 3.11 (2H, t, J = 7.1 Hz).

Step 2

Synthesis of 2,10-dimethoxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Step 4 of Example 1, the title compound (1 g, 77 %) was obtained from the compound obtained in Step 1 (1 g).

Example 264

Synthesis of 2,10-dichloro-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of N-(4-chlorophenyl)-β-alanine

To p-chloroaniline (200 g) suspended in water (100 ml) was added acrylic acid (54.1 ml) and the mixture heated under reflux for two hours under a nitrogen atmosphere. After allowing to cool, 2N sodium hydroxide aqueous solution (500 ml) was added, and extraction with ether was carried out. The aqueous layer was made pH3 with 1N hydrochloric acid and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (137.3 g, 87 %) was obtained without refining.

mp.: 119.0-121.0°C

IR spectrum (KBr tablet) ν cm^{-1}: 1707, 1599, 1508, 1435, 1329, 1219, 816
NMR spectrum (*DMSO-d_6) δ ppm: 7.08 (2H, d, J = 8.9 Hz), 6.56 (2H, d, J = 8.9 Hz), 5.83 (1H, bs), 3.21 (2H, t, J = 6.8 Hz), 2.50-2.45 (2H, m).

Step 2

Synthesis of 6-chloro-2,3-dihydro-4(1H)-quinolinone

The compound obtained in Step 1 (137 g) was added to polyphosphoric acid (2147 g) and the mixture stirred under heating at 120°C-130°C on an oil bath for 1 hour. The reaction liquor was discharged into iced water (4 l) and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (83.5 g, 66 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: hexane : ethyl acetate = 1 : 2).
mp.: 124.8-129.8°C
IR spectrum (KBr tablet) ν cm^{-1}: 3348, 1648, 1613, 1512, 1398, 1294, 1167, 814
NMR spectrum (*DMSO-d_6) δ ppm: 7.49 (1H, d, J = 2.6 Hz), 7.29 (1H, dd, J = 9.6, 2.6 Hz), 7.02 (1H, s), 6.80 (1H, d, J = 9.6 Hz), 3.46-3.41 (2H, m), 2.56-2.54 (2H, m).

Step 3

Synthesis of 6-chloro-1-(4-chlorophenyl)-2, 3-dihydro-4(1H)-quinolinone

The compound obtained in Step 2 (9.02 g), 1-chloro-4-iodobenzene (23.7 g), copper (II) oxide (1.04 g) and potassium carbonate (6.87 g) were mixed and the mixture stirred under an argon atmosphere under heating at 180-190°C on an oil bath for 6 hours. The reaction liquor was poured into iced water and extraction with ether was carried out. The insolubles were separated by filtration, and the ether layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (5.3 g, 36 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: hexane : methylene chloride = 1 : 2).
mp.: 142.8-149.5°C
IR spectrum (KBr tablet) ν cm^{-1}: 1677, 1490, 1475, 1209, 1166, 825.
NMR spectrum (*DMSO-d_6) δ ppm: 7.82 (1H, d, J = 8.6 Hz), 7.67 (2H, d, J = 2.7 Hz), 7.41-7.39 (1H, m), 7.37-7.36 (1H, m), 7.33 (1H, dd, J = 9.1, 2.7 Hz), 6.62 (1H, d, J = 9.1 Hz), 3.90 (2H, t, J = 6.9 Hz), 2.80 (2H, t, J = 6.9 Hz).

Step 4

Synthesis of 6-chloro-1-(4-chlorophenyl)-4(1H)-quinolinone

The compound obtained in Step 3 (1 g) was dissolved in 10 ml ethylene glycol and 5 % palladium carbon (200 mg) was added and the mixture heated under reflux under an argon atmosphere for 30 minutes. After allowing to cool, the insolubles were separated by filtration, and the filtrate was concentrated down by distillation under reduced pressure. The title compound (120 mg, 12 %) was obtained by refining the residue by silica gel column chromatography (eluting solvent: hexane : ethyl acetate = 1 : 1).

mp.: 236.3-237.5°C

IR spectrum (KBr tablet) ν cm^{-1}: 1632, 1587, 1493, 1471, 1293, 825

NMR spectrum (DMSO-d_6) δ ppm: 8.14 (1H, d, J = 2.6 Hz), 8.02 (1H, d, J = 7.6 Hz), 7.75-7.72 (2H, m), 7.67-7.63 (3H, m), 7.05 (1H, d, J = 9.2 Hz), 6.22 (1H, d, J = 7.6 Hz).

Step 5

Synthesis of 2,10-dichloro-4H-pyrido [3,2,1-jk] carbazol-4-one

6-chloro-1-(4-chlorophenyl)-4(1H)-quinolinone (2 g) obtained in Step 4 was dissolved in acetic acid (150 ml), and boron trifluoride acetic acid complex (44 ml) and palladium diacetate (6.28 g) were added and the mixture heated under reflux under an argon atmosphere for 1 hour. After allowing to cool, the insolubles were separated by filtration and extraction was carried out with water and ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (40 mg, 2 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: hexane : ethyl acetate = 1 : 2).

Example 265

Synthesis of 5-benzyl-2,10-dichloro-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 3,6-dichloro carbazole

The title compound (29 g, 41 %) was obtained from commercial carbazole (50 g) in accordance with Step 2 of Example 243.

mp.: 206.5-208.6°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3406, 1477, 1464, 1286, 1078, 810, 571.

NMR spectrum (DMSO-d_6) δ ppm: 11.59 (1H, s), 8.30 (2H, d, J = 2.0 Hz), 7.52 (2H, d, J = 8.7 Hz), 7.42 (2H, dd, J = 8.7, 2.0 Hz).

Step 2

Synthesis of 2,10-dichloro-5,6-dihydro-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound was obtained from the compound obtained in Step 1 according to the procedures of Step 2 and Step 3 of Example 1.

mp.: 248.5-252.1°C.

IR spectrum (KBr tablet) ν cm^{-1}: 1683, 1495, 1470, 1323, 1213, 791

NMR spectrum (DMSO-d_6) δ ppm: 8.59 (1H, d, J = 2.0 Hz), 8.42 (1H, d, J = 2.3 Hz), 7.77-7.73 (2H, m), 7.61 (1H, dd, J = 8.6, 2.0 Hz), 4.62 (2H, t, J = 7.0 Hz), 3.16 (2H, t, J = 7.0 Hz).

Step 3

Synthesis of 5-benzyl-2,10-dichloro-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (508 mg, 81 %) was obtained from the compound obtained in Step 2 (500 mg) in accordance with Example 90.

Example 271

Synthesis of 5-(4-aminobenzyl)-2,10-dichloro-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound (1.5 g) obtained in Example 270 was suspended in a mixed solvent of tetrahydrofuran (500 ml) and water (200 ml), and hydrobromic acid (48 %, 200 ml) was added and the mixture was heated under reflux under an argon atmosphere for 39 hours. After allowing to cool, the solvent was eliminated by distillation under reduced pressure to about half the quantity, and thereafter, 1N sodium hydroxide was added and the pH adjusted to pH7. The precipitated crystals were recovered by filtration, and the title compound (860 mg, 74 %) was obtained by washing successively with methanol and ether.

Example 272

Synthesis of 2-chloro-10-nitro-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 3-chloro carbazole-N-β-propionitrile

3-chloro carbazole (3 g) prepared using a process in accordance with the literature (Rec Trav Chim, 73, 197 (1954)) was suspended in 7.06 ml acrylonitrile and Triton B (0.1 ml) was added dropwise under ice cooling. A suitable quantity of methanol was added after stirring for 15 minutes, and the title compound (3.7 g, 98 %) was obtained by recovering the precipitated crystals by filtration.

mp.: 164.7-166.3°C

IR spectrum (KBr tablet) ν cm^{-1}: 1473, 1456, 1275, 1200, 806, 744.

NMR spectrum (DMSO-d_6) δ ppm: 8.29 (1H, d, J = 2.3 Hz), 8.22 (1H, d, J = 7.9 Hz), 7.79-7.73 (2H, m), 7.51-7.50 (2H, m), 7.28-7.22 (1H, m), 4.76 (2H, t, J = 6.6 Hz), 3.04 (2H, t, J = 6.6 Hz).

Step 2

Synthesis of 3-chloro-6-nitro carbazole-N-β-propionitrile

The compound obtained in Step 1 (3.5 g) was dissolved in 31 ml nitrobenzene, and fuming nitric acid (1.25 ml) was added at room temperature and the mixture stirred for 1 hour. The crystals were recovered by filtration, and the title compound (2.67 g, 65 %) was obtained by washing successively with methanol and ether.

mp.: 326.2°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 1510, 1479, 1336, 1321, 1296, 1097

NMR spectrum (DMSO-d_6) δ ppm: 9.30 (1H, d, J = 2.3 Hz), 8.61 (1H, d, J = 2.0 Hz), 8.40 (1H, d, J = 9.1, 2.3 Hz), 7.98 (1H, d, J = 9.1 Hz), 7.91 (1H, d, J = 8.8 Hz), 7.63 (1H, d, J = 8.8, 2.0 Hz), 4.87 (2H, t, J = 6.6 Hz), 3.10 (2H, t, J = 6.6 Hz).

Step 3

Synthesis of 3-chloro-6-nitro carbazole-N-β-propionic acid

The compound obtained in Step 2 (3 g) was suspended in 40 ml ethanol, and 2N sodium hydroxide (40 ml) was added and the mixture was heated under reflux under an argon atmosphere for nine hours. After allowing to cool, the solvent was eliminated under reduced pressure, and thereafter water and ether were added and liquid separation was carried out. The aqueous layer was made acidic by the addition of 4N hydrochloric acid, and thereafter the thereby formed precipitate was recovered by

filtration, and the title compound (2.1 g, 66 %) was obtained by washing successively with methanol and ether.

mp.: 325.8°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 1713, 1508, 1477, 1338, 1323, 1298, 814

NMR spectrum (DMSO-d_6) δ ppm: 12.42 (1H, bs), 9.27 (1H, d, J = 2.3 Hz), 8.58 (1H, d, J = 2.0 Hz), 8.37 (1H, dd, J = 9.2, 2.3 Hz), 7.87 (1H, d, J = 9.2 Hz), 7.81 (1H, d, J = 8.8 Hz), 7.60 (1H, dd, J = 8.8, 2.0 Hz), 4.72 (2H, t, J = 6.6 Hz), 2.80 (2H, t, J = 6.6 Hz).

Step 4

Synthesis of 2-chloro-5,6-dihydro-10-nitro-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 3 (200 mg) was suspended in anhydrous methylene chloride (2.5 ml), and thionyl chloride (0.1 ml) and anhydrous dimethylformamide (one drop) were added under ice cooling and the mixture heated under reflux under an argon atmosphere for two hours. The reaction liquor was allowed to cool, and thereafter the solvent was eliminated by distillation under reduced pressure. The thereby obtained residue was suspended in anhydrous methylene chloride (2 ml), cooled on a dry ice-acetone bath, and aluminum chloride (167 mg) added and the mixture warmed to room temperature. The reaction liquor was discharged into iced water and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (94 mg, 50 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: 3 % methanol-containing methylene chloride).

mp.: 360.0°C (degradation).

IR spectrum (KBr tablet) ν cm^{-1}: 1686, 1603, 1510, 1329, 1302, 750

NMR spectrum (DMSO-d_6) δ ppm; 9.36 (1H, d, J = 2.4 Hz), 8.82 (1H, d, J = 1.7 Hz), 8.46 (1H, dd, J = 9.0, 2.4 Hz), 7.90 (1H, d, J = 9.0 Hz), 7.80 (1H, d, J = 1.7 Hz), 4.73 (2H, t, J = 7.1 Hz), 3.20 (2H, t, J = 7.1 Hz).

Step 5

Synthesis of 2-chloro-10-nitro-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound (2.3 g, 59 %) was obtained from the compound obtained in Step 4 (3 g) in accordance with Step 4 of Example 1.

Example 273

Synthesis of 10-amino-2-chloro-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

2-chloro-10-nitro-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (1.86 g) obtained in Example 272 was dissolved in concentrated sulfuric acid (11 ml), and copper (995 mg) was added, and the mixture heated to 50°C on a warm water bath and stirred for 30 minutes. After allowing to cool, the reaction liquor was discharged into iced water, and thereafter the pH was adjusted to pH10 with 1N sodium hydroxide aqueous solution, and the precipitated crystals were recovered by filtration, and the title compound (1.37 g, 80 %) was obtained by successively washing with water and ether.

Example 274

Synthesis of 2-chloro-10-hydroxy-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

10-amino-2-chloro-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (300 mg) obtained in Example 273 was dissolved in a mixed solvent of concentrated sulfuric acid (14.6 ml) and water (20 ml), and under ice cooling, sodium nitrite (63 mg) dissolved in water (1 ml) was added dropwise. A mixed solvent of concentrated sulfuric acid (20 ml) and water (15 ml) was heated under reflux under an argon atmosphere, the solution prepared beforehand was dropwise added and thereafter the mixture stirred for five minutes. After allowing to cool, the pH was adjusted to pH9 with 1N sodium hydroxide aqueous solution and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The title compound (213 mg, 71 %) was obtained by successively washing the residue with methanol and ether.

Example 276

Synthesis of 10-bromo-2-methyl-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 6-methyl-1,2,3,4-tetrahydrocarbazole

The title compound (27 g, 93 %) was obtained from the p-tolyl hydrazine hydrochloride (25 g) in accordance with Step 1 of Example 171.

mp.: 147.3-150.6°C

IR spectrum (KBr tablet) ν cm^{-1}: 3396, 2929, 1589, 1439, 1315, 797, 596.

NMR spectrum (DMSO-d_6) δ ppm: 10.45 (1H, s), 7.12 (1H, s), 7.11 (1H, d, J = 7.8 Hz), 6.78 (1H, dd, J = 7.8, 1.5 Hz), 2.69-2.65 (2H, m), 2.60-2.50 (2H, m), 2.34 (3H, s), 1.81-1.78 (4H, m).

Step 2

Synthesis of 3-methylcarbazol

The compound obtained in Step 1 (20 g) was dissolved in 500 ml xylene and 10 % palladium carbon (6 g) was added and the mixture heated under reflux under an argon atmosphere for five hours. The reaction liquor was filtered while heating, and from the filtrate, the solvent was eliminated by distillation under reduced pressure. The title compound (7.5 g, 38 %) was obtained by refining the residue by silica gel flash column chromatography (eluting solvent: hexane : ethyl acetate = 20 : 1).

mp.: 206.2-209.5°C

IR spectrum (KBr tablet) ν cm^{-1}: 3408, 1462, 1242, 806, 748, 729, 573.

NMR spectrum (DMSO-d_6) δ ppm: 11.09 (1H, s), 8.05 (1H, d, J = 7.8 Hz), 7.89 (1H, s), 7.44 (1H, d, J = 8.3 Hz), 7.38-7.32 (2H, m), 7.20 (1H, dd, J = 8.3, 1.5 Hz), 7.11 (1H, t, J = 6.8 Hz), 2.46 (3H, s).

Step 3

Synthesis of 3-bromo-6-methylcarbazol

In accordance with Step 3 of Example 235, the title compound (1.85 g, 64 %) was obtained from the compound obtained in Step 2 (2 g).

mp.: 211.7-212.6°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3394, 1491, 1444, 1296, 1240, 812, 569.

NMR spectrum (DMSO-d_6) δ ppm: 11.29 (1H, bs), 8.29 (1H, d, J = 2.0 Hz), 7.95 (1H, d, J = 1.2 Hz), 7.54-7.35 (3H, m), 7.24 (1H, dd, J = 8.3, 1.2 Hz), 2.45 (3H, s).

Step 4

Synthesis of 10-bromo-5,6-dihydro-2-methyl-4H-pyrido [3,2,1-jk] carbazol-4-one

The title compound was obtained from the compound obtained in Step 3 in accordance with Step 2 and Step 3 of Example 1.

mp.: 201.7-204.4°C.

IR spectrum (KBr tablet) ν cm^{-1}: 1670, 1597, 1498, 1477, 1281, 1221, 791

NMR spectrum ($CDCl_3$) δ ppm: 8.17 (1H, d, J = 1.6 Hz), 7.98 (1H, s), 7.77-7.76 (1H, m), 7.59 (1H, dd, J = 8.5, 1.6 Hz), 7.26 (1H, s), 4.46 (2H, t, J = 7.1 Hz), 3.15 (2H, t, J = 7.1 Hz), 2.55 (3H, s).

Step 5

Synthesis of 10-bromo-2-methyl-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Title compound (120 mg, 47 %) was obtained from the compound obtained in Step 4 (2 g) in

accordance with Step 4 of Example 1.

Example 278

Synthesis of 9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one hydrochloride

9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (300 mg) obtained in Example 110 was suspended in 10 ml methanol, and under ice cooling, hydrochloric acid • methanol solution (5 ml) was added and the mixture stirred for five minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter the thereby obtained crude crystals were washed with ether, and the title compound (320 mg, 98 %) was obtained.

mp.: 201.1-204.2°C

IR spectrum (KBr tablet) ν cm^{-1}: 3369, 1578, 1508, 1464, 1389

NMR spectrum (*DMSO-d_6) δ ppm: 9.21 (1H, s), 8.95 (1H, s), 8.76 (1H, d, J = 5.5 Hz), 8.54 (1H, d, J = 8.1 Hz), 8.38 (1H, d, J = 1.6 Hz), 8.28-8.19 (2H, m), 7.95 (1H, dd, J = 8.1, 5.5 Hz), 7.65 (1H, dd, J = 8.3, 1.6 Hz), 7.53 (1H, d, J = 1.6 Hz), 4.22 (2H, t, J = 6.3 Hz), 4.06 (2H, s), 3.62 (2H, t, J = 6.1 Hz), 2.07-1.89 (2H, m).

Example 279

Synthesis of 9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one methanesulfonate

9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridyl methyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (250 mg) obtained in Example 110 was suspended in 200 ml methanol, and a methanol solution (5 ml) of methanesulfonate (57 mg) was added at room temperature and the mixture stirred for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter the thereby obtained crude crystals were washed successively with a small amount of methanol and ether, and the title compound (270 mg, 89 %) was obtained.

mp.: 243.9-250.7°C

IR spectrum (KBr tablet) ν cm^{-1}: 3388, 1572, 1510, 1209, 1192, 1055

NMR spectrum (*DMSO-d_6) δ ppm: 9.19 (1H, s), 8.96-8.91 (1H, m), 8.75 (1H, d, J = 5.5 Hz), 8.50 (1H, d, J = 8.1 Hz), 8.40 (1H, d, J = 1.4 Hz), 8.27 (1H, d, J = 2.2 Hz), 8.24 (1H, d, J = 8.3 Hz), 7.96-7.89 (1H, m), 7.67 (1H, dd, J = 8.3, 1.4 Hz), 7.54 (1H, d, J = 2.2 Hz), 4.22 (2H, t, J = 6.3 Hz), 4.06 (2H, s), 3.62 (2H, t, J = 6.1 Hz), 2.32 (3H, s), 2.02-1.88 (2H, m).

Example 280

Synthesis of 9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one nitrate

9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (50 mg) obtained in Example 110 was suspended in 100 ml methanol, and a methanol solution (5 ml) of nitric acid (11 mg) was added at room temperature and the mixture stirred for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter the crude crystals thereby obtained were washed successively with a small amount of methanol and ether, and the title compound (47 mg, 83 %) was thereby obtained.

mp.: 200.2-202.4°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3371, 1572, 1462, 1385, 1333

NMR spectrum (*DMSO-d_6) δ ppm: 9.18 (1H, s), 8.93 (1H, s), 8.75 (1H, d, J = 5.7 Hz), 8.51 (1H, d, J = 7.9 Hz), 8.39 (1H, d, J = 1.5 Hz), 8.27 (1H, d, J = 2.2 Hz), 8.24 (1H, d, J = 8.4 Hz), 7.97-7.88 (1H, m), 7.67 (1H, dd, J = 8.4, 1.5 Hz), 7.54 (1H, d, J = 2.2 Hz), 4.22 (2H, t, J = 6.4 Hz), 4.06 (2H, s), 3.62 (2H, t, J = 6.1 Hz), 2.03-1.88 (2H, m).

Example 281

Synthesis of 9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one sulfate

9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (50 mg) obtained in Example 110 was suspended in 100 ml methanol, and a methanol solution (5 ml) of sulphuric acid (6×10^{-3} ml) was added at room temperature and the mixture stirred for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter, the crude crystals thereby obtained were washed successively with a small amount of methanol and ether, and the title compound (49 mg, 81 %) was obtained.

mp.: >300°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3388, 1564, 1512, 1389, 1225, 1188, 1059

NMR spectrum (*DMSO-d_6) δ ppm: 9.18 (1H, s), 8.96-8.90 (1H, m), 8.75 (1H, d, J = 5.7 Hz), 8.51 (1H, d, J = 8.3 Hz), 8.40 (1H, d, J = 1.4 Hz), 8.27 (1H, d, J = 2.1 Hz), 8.24 (1H, d, J = 8.2 Hz), 7.97-7.89 (1H, m), 7.68 (1H, dd, J = 8.2, 1.4 Hz), 7.54 (1H, d, J = 2.1 Hz), 4.22 (2H, t, J = 6.3 Hz), 4.06 (2H, s), 3.62 (2H, t, J = 6.2 Hz), 2.02-1.89 (2H, m).

Example 282

Synthesis of 9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one maleate

9-bromo-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one (50 mg) obtained in Example 110 was suspended in 100 ml methanol, a methanol solution (5 ml) of maleic acid (2.5 mg) was added at room temperature, and the mixture was stirred while heating under reflux for 30 minutes. After allowing to cool, the solvent was eliminated by distillation under reduced pressure, and thereafter, the crude crystals thereby obtained were washed successively with a small amount of methanol and ether, and the title compound (50 mg, 80 %) obtained.

mp.: 188.4-191.4°C

IR spectrum (KBr tablet) ν cm^{-1}: 3365, 1595, 1576, 1510, 1462, 1389

NMR spectrum (*DMSO-d_6) δ ppm: 9.17 (1H, s), 8.71-8.65 (1H, m), 8.49-8.40 (2H, m), 8.28-8.21 (2H, m), 7.90 (1H, d, J = 8.3 Hz), 7.65 (1H, dd, J = 8.3, 1.0 Hz), 7.56 (1H, d, J = 2.0 Hz), 7.44-7.36 (1H, m), 6.22 (2H, s), 4.23 (2H, t, J = 6.5 Hz), 3.91 (2H, s), 3.62 (2H, t, J = 6.5 Hz), 2.00-1.89 (2H, m).

Example 283

Synthesis of 9-chloro-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

Step 1

Synthesis of 2-chloro-6-[3-(4-methoxyphenoxy) propyloxy] carbazole

2-chloro-6-hydroxycarbazole (14.2 g) prepared using a process in accordance with the literature (Justus Liebigs Ann. Chem, 617, 54 (1958)) was dissolved in 140 ml methanol, and 2N potassium hydroxide methanol solution (36.7 ml) was added at room temperature, and the mixture was stirred at room temperature for five minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter toluene (40 ml) was added and the solvent eliminated by distillation under reduced pressure once again. The thereby obtained crystals were suspended in 53 ml toluene, and thereto were added toluene (18 ml) in which was dissolved 3-(4-methoxyphenoxy) propyl bromide (18.0 g) prepared using a process in accordance with the literature (Kokai Tokkyo Koho JP 02193942) and toluene (18 ml) in which was dissolved 18-crown-6 (1.9 g), and the mixture was heated under reflux for 1 hour. After allowing to cool, 0.001N hydrochloric acid (120 ml) was added and extraction with ethyl acetate was carried out. The ethyl acetate layer was washed with saturated aqueous sodium

chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in acetone, reprecipitated with methanol : water = 1 : 1 and thereafter caused to dissolve in methylene chloride. and silica gel was added. Thereafter the solvent was eliminated by distillation under reduced pressure, and the title compound (15.7 g, 56 %) was obtained by elution with hexane : methylene chloride = 1 : 1 solution from this adsorbed state on the silica gel and elimination of the solvent by distillation under reduced pressure.

mp.: 137.1-138.7°C

IR spectrum (KBr tablet) ν cm^{-1}: 3396, 1508, 1456, 1294, 1201, 1031, 823

NMR spectrum (*DMSO-d_6) δ ppm: 11.21 (1H, s), 8.12 (1H, d, J = 2.3 Hz), 7.73 (1H, d, J = 2.3 Hz), 7.47 (1H, d, J = 1.8 Hz), 7.40 (1H, d, J = 8.7 Hz), 7.12 (1H, dd, J = 8.3, 1.8 Hz), 7.06 (1H, dd, J = 8.7, 2.3 Hz), 6.95-6.82 (4H, m), 4.21 (2H, t, J = 6.2 Hz), 4.11 (2H, t, J = 6.1 Hz), 3.69 (3H, s), 2.25-2.13 (2H, m).

Step 2

Synthesis of 2-chloro-6-[3-(4-methoxyphenoxy) propyloxy] carbazole-N-β-propionic acid

The compound obtained in Step 1 (15.7 g) was dissolved in 630 ml acetone, and under ice cooling, thereto were added dropwise methyl acrylate (4.6 g) and then Triton B (3.7 ml). The mixture was stirred for 1 hour, and thereafter the solvent was eliminated by distillation under reduced pressure. The thereby obtained residue was suspended in 94 ml methanol, and sodium hydroxide (3.3 g) dissolved in water (4.4 ml) was added dropwise, and the mixture was stirred at 60°C on a warm water bath for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter the residue was decanted with ether, 1N hydrochloric acid and ethyl acetate were added to the crystals obtained and liquid separation was carried out. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure and the title compound (17.6 g, 94 %) was obtained.

mp.: 126.7-130.7°C

IR spectrum (KBr tablet) ν cm^{-1}: 2937, 1699, 1514, 1489, 1238, 1072, 822

NMR spectrum (*DMSO-d_6) δ ppm: 12.34 (1H, bs), 8.12 (1H, d, J = 8.4 Hz), 7.77 (1H, d, J = 2.5 Hz), 7.71 (1H, d, J = 1.6 Hz), 7.54 (1H, d, J = 8.9 Hz), 7.20-7.18 (2H, m), 6.97-6.80 (4H, m), 4.58 (2H, t, J = 6.7 Hz), 4.22 (2H, t, J = 6.2 Hz), 4.11 (2H, t, J = 6.2 Hz), 3.69 (3H, s), 2.71 (2H, t, J = 6.7 Hz), 2.26-2.13 (2H, m).

Step 3

Synthesis of 9-chloro-5,6-dihydro-2-[3-(4-methoxyphenoxy) propyloxy]-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 2 (14.6 g) was suspended in anhydrous chloroform (400 ml), and PPE (83.2 g) dissolved in anhydrous chloroform (400 ml) was added at room temperature and the mixture heated under reflux under an argon atmosphere for 1 hour 30 minutes. After allowing to cool, the reaction liquor was discharged into water and extraction with methylene chloride was carried out. The methylene chloride layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was crystallized with acetone : methanol = 1 : 1 and recovered by filtration, thereafter the crude crystals were dissolved with chloroform while heating, and the title compound (6.3 g, 38 %) was obtained by reprecipitating using methanol.

mp.: 156.3-159.0°C

IR spectrum (KBr tablet) ν cm^{-1}: 2953, 1680, 1506, 1443, 1228, 1065, 818

NMR spectrum (*DMSO-d_6) δ ppm: 8.20 (1H, d, J = 8.3 Hz), 8.11 (1H, d, J = 2.2 Hz), 7.80 (1H, d, J = 1.7 Hz), 7.35 (1H, d, J = 2.2 Hz), 7.25 (1H, dd, J = 8.3, 1.7 Hz), 6.94-6.77 (4H, m), 4.54 (2H, t, J = 7.0 Hz), 4.24 (2H, t, J = 6.1 Hz), 4.10 (2H, t, J = 6.1 Hz), 3.67 (3H, s), 3.10 (2H, t, J = 7.0 Hz), 2.24-2.12 (2H, m).

Step 4

Synthesis of 9-chloro-2-[3-(4-methoxyphenoxy) propyloxy]-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 3 (6.3 g) was suspended in 410 ml ethanol, and pyridin-3-aldehyde (2.5 g) and sodium hydroxide (4.6 g) dissolved in water (25 ml) were added, and the mixture was stirred at 60°C on a warm water bath for 15 minutes. The solvent was eliminated by distillation under reduced pressure and thereafter the crystals were washed with water. The obtained crude crystals were dissolved with acetonitrile : water = 20 : 1 solution while heating, and the title compound (6.7 g, 87 %) was obtained by reprecipitating with water.

mp.: 157.0-160.9°C

IR spectrum (KBr tablet) ν cm^{-1}: 3431, 2933, 1605, 1508, 1462, 1232, 1064

NMR spectrum (*DMSO-d_6) δ ppm: 9.10 (1H, s), 8.66-8.60 (1H, m), 8.42-8.35 (1H, m), 8.25 (1H, d, J = 1.8 Hz), 8.22 (1H, d, J = 8.2 Hz), 8.19 (1H, d, J = 2.2 Hz), 7.79-7.70 (1H, m), 7.53 (1H, d, J = 2.2 Hz), 7.47 (1H, dd, J = 8.2, 1.8 Hz), 7.32-7.23 (1H, m), 6.95-6.78 (4H, m), 4.29 (2H, t, J = 6.2

Hz), 4.11 (2H, t, J = 6.1 Hz), 3.86 (2H, s), 3.66 (3H, s), 2.28-2.14 (2H, m).

Step 5

Synthesis of 9-chloro-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

The compound obtained in Step 4 (3.7 g) was suspended in a solution (400 ml) of acetonitrile : water = 4 : 1, and CAN (11.5 g) dissolved in a solution (40 ml) of acetonitrile : water = 4 : 1 was added slowly dropwise while ice-cooling, and after stirring for 15 minutes, 1N sodium hydroxide aqueous solution was added. The precipitated crystals were recovered by filtration and washed with a small amount of water. These crude crystals were added to ethyl acetate and the mixture stirred for 3 hours, and the insolubles were separated by filtration. The filtrate was washed successively with 10 % sodium sulfite aqueous solution, 1N sodium hydroxide aqueous solution and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure. The thereby obtained crystals were washed with ether, and the title compound (1.3 g, 46 %) was obtained by recovering by filtration.

mp.: 213.9-220.8°C

IR spectrum (KBr tablet) ν cm^{-1}: 3429, 1597, 1506, 1462, 1389, 1234, 1065.

NMR spectrum (*DMSO-d_6) δ ppm: 9.15 (1H, s), 8.66-8.60 (1H, m), 8.42-8.35 (1H, m), 8.35-8.18 (3H, m), 7.80-7.73 (1H, m), 7.54 (1H, d, J = 2.2 Hz), 7.51 (1H, dd, J = 8.3, 1.8 Hz), 7.33-7.24 (1H, m), 4.63 (1H, t, J = 5.0 Hz), 4.22 (2H, t, J = 6.4 Hz), 3.88 (2H, s), 3.69-3.55 (2H, m), 2.03-1.88 (2H, m).

Example 284

Synthesis of 9-chloro-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one hydrochloride

In accordance with Example 278, the title compound (55 mg, 85 %) was obtained from the compound obtained in Example 283 (60 mg).

mp.: 199.3-202.7°C

IR spectrum (KBr tablet) ν cm^{-1}: 3396, 1605, 1578, 1510, 1462, 1390, 1066

NMR spectrum (*DMSO-d_6) δ ppm: 9.20 (1H, s), 8.92 (1H, s), 8.73 (1H, d, J = 5.3 Hz), 8.48 (1H, d, J = 8.1 Hz), 8.30 (1H, d, J = 8.3 Hz), 8.30-8.22 (2H, m), 7.94-7.85 (1H, m), 7.58-7.47 (2H, m), 4.22 (2H, t, J = 6.3 Hz), 4.05 (2H, s), 3.62 (2H, t, J = 6.1 Hz), 2.02-1.88 (2H, m).

Example 285

Synthesis of 9-chloro-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one methanesulfonate

In accordance with Example 279, the title compound (696 mg, 73 %) was obtained from the compound obtained in Example 283 (780 mg).

mp.: 215.7-221.6°C

IR spectrum (KBr tablet) ν cm^{-1}: 3431, 1605, 1510, 1462, 1390, 1211, 1039

NMR spectrum (*DMSO-d_6) δ ppm: 9.18 (1H, s), 8.92 (1H, s), 8.74 (1H, d, J = 5.3 Hz), 8.48 (1H, d, J = 7.9 Hz), 8.31 (1H, d, J = 8.4 Hz), 8.30-8.22 (2H, m), 7.91 (1H, dd, J = 7.9, 5.3 Hz), 7.60-7.51 (2H, m), 4.22 (2H, t, J = 6.5 Hz), 4.05 (2H, s), 3.62 (2H, t, J = 6.2 Hz), 2.31 (3H, s), 2.00-1.89 (2H, m).

Example 286

Synthesis of 9-fluoro-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Step 1, Step 2, Step 3, Step 4 and Step 5 of Example 283, the title compound was obtained from the commercial 4-fluoro-2-nitroaniline.

mp.: 204.5-208.7°C.

IR spectrum (KBr tablet) ν cm^{-1}: 1593, 1574, 1512, 1464, 1205, 1097, 847

NMR spectrum (*DMSO-d_6) δ ppm: 9.09 (1H, s), 8.63 (1H, d, J = 2.2 Hz), 8.40-8.38 (1H, m), 8.29 (1H, dd, J = 8.5, 5.3 Hz), 8.19 (1H, d, J = 2.0 Hz), 8.05 (1H, dd, J = 9.5, 2.2 Hz), 7.80-7.71 (1H, m), 7.50 (1H, d, J = 2.0 Hz), 7.38-7.22 (2H, m), 4.62 (1H, t, J = 5.1 Hz), 4.22 (2H, t, J = 6.2 Hz), 3.89 (2H, s), 3.71-3.57 (2H, m), 2.05-1.88 (2H, m).

Example 287

Synthesis of 9-fluoro-2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one methanesulfonate

In accordance with Example 279, the title compound (750 mg, 87 %) was obtained from the compound obtained in Example 286 (700 mg).

mp.: 198.5-203.6°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3032, 1593, 1514, 1464, 1392, 1201, 1039

NMR spectrum (*DMSO-d8) δ ppm: 9.13 (1H, s), 8.95 (1H, s), 8.77 (1H, d, J = 5.2 Hz), 8.55 (1H, d, J = 8.1 Hz), 8.31 (1H, dd, J = 8.7, 5.4 Hz), 8.21 (1H, d, J = 2.2 Hz), 8.01 (1H, dd, J = 9.5, 2.2 Hz),

8.00-7.91 (1H, m), 7.48 (1H, d, J = 2.2 Hz), 7.41-7.29 (1H, m), 4.21 (2H, t, J = 6.2 Hz), 4.07 (2H, s), 3.62 (2H, t, J = 6.2 Hz), 2.34 (3H, s), 2.01-1.88 (2H, m).

Example 288

Synthesis of 2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Example 105, the title compound (82 mg, 69 %) was obtained from the compound obtained in Example 155 (100 mg) and 3-bromo-1-propanol (83 ml).

mp.: 72.5-78.6°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3400, 1568, 1510, 1458, 1335, 1309

NMR spectrum (*DMSO-d_6) δ ppm: 9.15 (1H, s), 8.68-8.61 (1H, m), 8.38 (1H, dd, J = 4.7, 1.6 Hz), 8.28 (1H, d, J = 7.5 Hz), 8.21 (1H, d, J = 2.2 Hz), 8.10 (1H, d, J = 8.3 Hz), 7.82-7.73 (1H, m), 7.70-7.61 (1H, m), 7.53 (1H, d, J = 2.2 Hz), 7.51-7.42 (1H, m), 7.28 (1H, dd, J = 7.7, 4.9 Hz), 4.63 (1H, t, J = 5.1 Hz), 4.23 (2H, t, J = 6.3 Hz), 3.91 (2H, s), 3.68-3.54 (2H, m), 2.02-1.88 (2H, m).

Example 289

Synthesis of 2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-9-trifluoromethyl-4H-pyrido [3,2,1-jk] carbazol-4-one

In accordance with Step 1, Step 2, Step 3, Step 4 and Step 5 of Example 283, the title compound was obtained from commercial 4-trifluoromethyl-2-nitroaniline.

mp.: 194.2-198.0°C.

IR spectrum (KBr tablet) ν cm^{-1}: 3213, 1605, 1574, 1471, 1389, 1346, 1321, 1161, 1117

NMR spectrum (*DMSO-d_6) δ ppm: 9.32 (1H, s), 8.70-8.64 (1H, m), 8.61 (1H, s), 8.51 (1H, d, J = 8.5 Hz), 8.42-8.33 (2H, m), 7.82 (1H, d, J = 8.5 Hz), 7.83-7.75 (1H, m), 7.63 (1H, d, J = 2.2 Hz), 7.29 (1H, dd, J = 8.0, 4.7 Hz), 4.62 (1H, t, J = 5.0 Hz), 4.25 (2H, t, J = 6.4 Hz), 3.90 (2H, s), 3.69-3.58 (2H, m), 2.03-1.90 (2H, m).

Example 290

Synthesis of 2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-9-trifluoromethyl-4H-pyrido [3,2,1-jk] carbazol-4-one hydrochloride

In accordance with Example 278, the title compound (57 mg, 89 %) was obtained from the compound obtained in Example 289 (60 mg).

mp.: 185.6-189.3°C

IR spectrum (KBr tablet) ν cm^{-1}: 3429, 1651, 1574, 1470, 1346, 1319, 1119

NMR spectrum (*DMSO-d_6) δ ppm: 9.36 (1H, s), 8.88 (1H, s), 8.67 (1H, d, J = 5.5 Hz), 8.58 (1H, s), 8.54 (1H, d, J = 7.7 Hz), 8.41 (1H, d, J = 2.0 Hz), 8.40-8.32 (1H, m), 7.89-7.75 (2H, m), 7.63 (1H, d, J = 2.0 Hz), 4.25 (2H, t, J = 6.2 Hz), 4.04 (2H, s), 3.62 (2H, t, J = 6.2 Hz), 2.04-1.89 (2H, m).

Example 291

Synthesis of 2-(3-hydroxy propyloxy)-5-(3-pyridylmethyl)-9-trifluoromethyl-4H-pyrido [3,2,1-jk] carbazol-4-one methanesulfonate

In accordance with Example 279, the title compound (683 mg, 94 %) was obtained from the compound obtained in Example 289 (600 mg).

mp.: 204.2-211.1°C

IR spectrum (KBr tablet) ν cm^{-1}: 3402, 1620, 1574, 1471, 1319, 1207, 1057

NMR spectrum (*DMSO-d_6) δ ppm: 9.36 (1H, s), 8.90 (1H, s), 8.75-8.64 (1H, m), 8.57 (1H, s), 8.54 (1H, d, J = 7.9 Hz), 8.46-8.37 (2H, m), 7.92-7.77 (2H, m), 7.62 (1H, d, J = 2.2 Hz), 4.25 (2H, t, J = 6.6 Hz), 4.05 (2H, s), 3.62 (2H, t, J = 6.2 Hz), 2.30 (3H, s), 2.01-1.90 (2H, m).

Table 4 shows the Example numbers of the compounds synthesized in accordance with each process described in the Examples.

Table 4

Compounds synthesized in accordance with Step 1 of Example 1

Example 185, Example 188, Example 252, Example 255.

Compounds synthesized in accordance with Step 4 of Example 1

Example 127, Example 128, Example 129, Example 130, Example 131, Example 133, Example 135, Example 136, Example 137, Example 138, Example 139, Example 140, Example 141, Example 142, Example 143, Example 144.

Compounds synthesized in accordance with Example 2

Example 132, Example 155, Example 186, Example 204, Example 211, Example 217, Example 225, Example 233, Example 236, Example 244, Example 249, Example 258, Example 269.

Compounds synthesized in accordance with Example 3

Example 10, Example 12, Example 13, Example 159.

Compounds synthesized in accordance with Example 5

Example 157, Example 206, Example 219, Example 227, Example 245, Example 250, Example 254.

Compounds synthesized in accordance with Example 6

Example 9, Example 11, Example 134, Example 158, Example 160.

Compounds synthesized in accordance with Example 14

Example 15, Example 16.

Compounds synthesized in accordance with Example 18

Example 19, Example 20, Example 21, Example 23, Example 251.

Compounds synthesized in accordance with Example 26

Example 27, Example 28, Example 29, Example 30, Example 31.

Compounds synthesized in accordance with Example 34

Example 35, Example 36, Example 37.

Compounds synthesized in accordance with Example 38

Example 156, Example 205, Example 212, Example 218, Example 226, Example 234, Example 237, Example 259.

Compounds synthesized in accordance with Example 39

Example 40, Example 42.

Compound synthesized in accordance with Example 44

Example 45.

Compound synthesized in accordance with Example 48

Example 152.

Compound synthesized in accordance with Example 49

Example 162.

Compound synthesized in accordance with Example 52

Example 164.

Compound synthesized in accordance with Example 53

Example 165.

Compounds synthesized in accordance with Example 56

Example 163, Example 183, Example 209, Example 215, Example 222, Example 230, Example 241.

Compounds synthesized in accordance with Example 58

Example 169, Example 187, Example 200, Example 207, Example 213, Example 220, Example 228, Example 239.

Compounds synthesized in accordance with Example 59

Example 170, Example 189, Example 208, Example 214, Example 221, Example 229, Example 240, Example 247, Example 261, Example 263.

Compounds synthesized in accordance with Example 62

Example 223, Example 231.

Compounds synthesized in accordance with Example 64

Example 65, Example 66, Example 67, Example 68, Example 69, Example 76, Example 77, Example 78.

Compound synthesized in accordance with Example 70

Example 72.

Compounds synthesized in accordance with Example 79

Example 80, Example 81.

Compounds synthesized in accordance with Example 84

Example 87, Example 90, Example 92, Example 94, Example 196, Example 260.

Compounds synthesized in accordance with Example 85

Example 88, Example 91, Example 93, Example 96.

Compound synthesized in accordance with Example 86

Example 89.

Compounds synthesized in accordance with Example 95

Example 153, Example 166, Example 191, Example 192.

Compound synthesized in accordance with Example 96

Example 167.

Compound synthesized in accordance with Example 97

Example 168.

Compound synthesized in accordance with Example 105

Example 106, Example 111.

Compound synthesized in accordance with Example 115

Example 118, Example 120.

Compound synthesized in accordance with Step 4 of Example 171

Example 180.

Compound synthesized in accordance with Example 179

Example 181, Example 182.

Compound synthesized in accordance with Example 195

Example 197, Example 201.

Compound synthesized in accordance with Example 198

Example 202.

Compound synthesized in accordance with Example 238

Example 242.

Compound synthesized in accordance with Step 3 of Example 243

Example 246.

Compound synthesized in accordance with Example 253

Example 256.

Compound synthesized in accordance with Step 1 of Example 257

Example 262.

Compound synthesized in accordance with Example 264

Example 275.

Compound synthesized in accordance with Step 3 of Example 265

Example 266, Example 267, Example 268, Example 270.

Compound synthesized in accordance with Step 4 of Example 276

Example 277.

The data for the physical properties of the compound of Examples 1-277 are shown in Table 5, and the compound of Examples 1-277 and structural formula of Examples 279-291 are shown in Tables 6-17. Moreover, Example 278 and the structures of the intermediate in the Examples are shown in the Figures.

Table 5

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
1	1578, 1504, 1475, 1419, 1329	*DMSO-d6: 9. 07 (1H, s), 8. 63 (1H, d, J=1. 9Hz), 8. 50 (1H, d, J=2. 2Hz), 8. 38 (1H, dd, J=4. 6, 1. 9Hz), 8. 18 (1H, d, J=2. 2Hz), 8. 00 (1H, d, J=8. 7Hz), 7. 80~7. 75 (2H, m), 7. 53 (1H, d, J=2. 2Hz), 7. 30~7. 26 (1H, m), 3. 93 (3H, s), 3. 88 (2H, s)	240. 9-243. 5
2	3292, 1568, 1502, 1390, 1319, 795, 716	*DMSO-d6: 10. 16 (1H, bs), 9. 08 (1H, s), 8. 63 (1H, s), 8. 52 (1H, d, J=1. 9Hz), 8. 39 (1H, bs), 8. 04~8. 00 (2H, m), 7. 80~7. 75 (2H, m), 7. 49 (1H, d, J =2. 2Hz), 7. 28 (1H, dd, J=7. 6, 4. 9Hz), 3. 88 (2H, s)	345. 8 (decomposition)
3	3429, 1649, 1605, 1578, 1504, 1423, 1329, 1155	*DMSO-d6: 9. 14 (1H, s), 8. 63 (1H, s), 8. 58 (1H, d, J=1. 9Hz), 8. 39~8. 37 (1H, m), 8. 30 (1H, d, J=2. 3Hz), 8. 07 (1H, d, J=8. 9Hz), 7. 85~7. 74 (2H, m), 7. 52 (1H, d, J=2. 3Hz), 7. 30~7. 23 (1H, m), 4. 87 (2H, s), 3. 89 (2H, s), 1. 44 (9H, s)	183. 0-185. 0
4	3500, 3000, 1741, 1603, 1504, 1325, 1225	*DMSO-d6: 9. 12 (1H, s), 8. 65~8. 62 (1H, m), 8. 56 (1H, d, J=1. 9Hz), 8. 38 (1H, dd, J=4. 8, 1. 5Hz), 8. 30 (1H, d, J=2. 3Hz), 8. 05 (1H, d, J=8. 7Hz), 7. 84~7. 80 (1H, m), 7. 76 (1H, d, J=7. 9Hz), 7. 52 (1H, d, J=2. 3Hz), 7. 28 (1H, dd, J=7. 9, 4. 8Hz), 5. 07~4. 96 (3H, m), 3. 89 (2H, s), 1. 24~1. 18 (6H, m)	171. 3-173. 0
5	3500, 1747, 1605, 1578, 1504, 1327	DMSO-d6: 9. 14 (1H, s), 8. 63~8. 58 (2H, m), 8. 39~8. 37 (1H, m), 8. 32 (1H, d, J=2. 0Hz), 8. 07 (1H, d, J=8. 8Hz), 7. 83 (1H, dd, J=8. 8, 2. 0Hz), 7. 78~7. 74 (1H, m), 7. 54 (1H, d, J=2. 0Hz), 7. 30~7. 25 (1H, m), 5. 00 (2H, s), 4. 20 (2H, q, J=7. 1Hz), 3. 89 (2H, s), 1. 23 (3H, t, J=7. 1Hz)	222. 9 (decomposition)
6	3500, 1653, 1599, 1506, 1473, 1325	DMSO-d6: 9. 15 (1H, s), 8. 62~8. 60 (2H, m), 8. 38~8. 32 (2H, m), 8. 08 (1H, d, J=8. 8Hz), 7. 83 (1H, dd, J=8. 8, 2. 0Hz), 7. 76 (1H, d, J=7. 8Hz), 7. 53 (1H, d, J=2. 0Hz), 7. 28 (1H, dd, J=7. 8, 4. 9Hz), 4. 90 (2H, s), 3. 90 (2H, s)	226. 7 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
7	1738, 1608, 1502, 1471, 1439, 804, 712	*DMSO-d6: 9. 15 (1H, s), 8. 63 (1H, d, J=1. 6Hz), 8. 59 (1H, d, J=1. 9Hz), 8. 39~8. 37 (1H, m), 8. 34 (1H, d, J=2. 3Hz), 8. 07 (1H, d, J=8. 7Hz), 7. 84 (1H, dd, J=8. 7, 1. 9Hz), 7. 78~7. 73 (1H, m), 7. 55 (1H, d, J=2. 3Hz), 7. 30~7. 25 (1H, m), 5. 03 (2H, s), 4. 11 (2H, t, J=6. 6Hz), 3. 89 (2H, s), 1. 64~1. 57 (2H m), 0. 86 (3H, t, J=7. 5Hz)	177. 0-179. 3
8	3000, 1720, 1605, 1470, 1333, 1142	*DMSO-d6: 9. 16 (1H, s), 8. 62 (1H, d, J=1. 6Hz), 8. 60 (1H, d, J=1. 9Hz), 8. 38 (1H, dd, J=4. 6, 1. 6Hz), 8. 22 (1H, d, J=2. 2Hz), 8. 08 (1H, d, J=8. 7Hz), 7. 84 (1H, dd, J=8. 7, 1. 9Hz), 7. 78~7. 74 (1H, m), 7. 50 (1H, d, J=2. 2Hz), 7. 28 (1H, dd, J=7. 9, 4. 9Hz), 4. 21 (2H, q, J=7. 1Hz), 3. 88 (2H, s), 1. 60 (6H, s), 1. 20 (3H, t, J=7. 1Hz)	163. 2-168. 4
9	3500, 1595, 1578, 1470, 1333, 1147	*DMSO-d6: 13. 20 (1H, bs), 9. 17 (1H, s), 8. 65 (1H, s), 8. 59 (1H, d, J=1. 9Hz), 8. 42~8. 40 (1H, m), 8. 24 (1H, d, J=2. 2Hz), 8. 08 (1H, d, J=8. 7Hz), 7. 86~7. 80 (2H, m), 7. 54 (1H, d, J=2. 2Hz), 7. 33 (1H, dd, J=7. 7, 4. 7Hz), 3. 90 (2H, s), 1. 59 (6H, s)	249. 4-251. 2
10	2900, 1716, 1649, 1605, 1508, 1327, 869	*DMSO-d6: 9. 04 (1H, s), 8. 63 (1H, d, J=1. 6Hz), 8. 46 (1H, d, J=1. 5Hz), 8. 38 (1H, dd, J=4. 7, 1. 5Hz), 8. 15~8. 12 (1H, m), 7. 98 (1H, d, J=8. 7Hz), 7. 78~7. 75 (2H, m), 7. 48 (1H, d, J=2. 2Hz), 7. 28 (1H, dd, J=7. 7, 4. 7Hz), 4. 16~4. 06 (4H, m), 3. 87 (2H, s), 2. 55~2. 51 (2H, m), 2. 09~2. 04 (2H, m), 1. 19 (3H, t, J=7. 2Hz)	159. 6-163. 8
11	3412, 1647, 1576, 1508, 1329, 715	*DMSO-d6: 9. 11 (1H, s), 8. 61 (1H, d, J=1. 6Hz), 8. 53 (1H, d, J=1. 9Hz), 8. 36 (1H, dd, J=4. 6, 1. 6Hz), 8. 26 (1H, d, J=2. 2Hz), 8. 04 (1H, d, J=8. 7Hz), 7. 82~7. 73 (2H, m), 7. 53 (1H, d, J=2. 2Hz), 7. 29~7. 27 (1H, m), 4. 15 (2H, t, J=6. 4Hz), 3. 88 (2H, s), 2. 38~2. 36 (2H, m), 2. 02~1. 98 (2H, m)	300. 0 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
12	1767, 1597, 1579, 1508, 1338, 1188	*DMSO-d6:9. 15 (1H, s), 8. 62 (1H, d, J=1. 5Hz), 8. 55 (1H, d, J=1. 8Hz), 8. 37 (1H, dd, J=4. 7, 1. 5Hz), 8. 31 (1H, d, J=2. 4Hz), 8. 06 (1H, d, J=8. 7Hz), 7. 83 (1H, dd, J=8. 7, 1. 8Hz), 7. 78~7. 72 (1H, m), 7. 57 (1H, d, J=2. 4Hz), 7. 34~7. 25 (6H, m), 5. 21 (2H, s), 5. 10 (2H s), 3. 88 (2H, s)	254. 0 (decomposition)
13	1759, 1603, 1574, 1504, 1325, 1225, 1174	*DMSO-d6:9. 14 (1H, s), 8. 65~8. 53 (2H, m), 8. 36 (1H, dd, J=4. 6, 1. 4Hz), 8. 32 (1H, d, 2. 3Hz), 8. 06 (1H, d, J=8. 8Hz), 7. 82 (1H, dd, J=8. 8, 2. 0Hz), 7. 74 (1H, d, J=7. 8Hz), 7. 54 (1H, d, J=2. 3Hz), 7. 26 (1H, dd, J=7. 8, 4. 6Hz), 5. 02 (2H, s), 3. 88 (2H, s), 3. 71 (3H, s)	270. 3 (decomposition)
14	2929, 1740, 1603, 1504, 1327, 1201, 1173	*DMSO-d6:9. 16 (1H, s), 8. 63 (1H, s), 8. 60~8. 58 (1H, m), 8. 39~8. 37 (1H, m), 8. 34 (1H, d, J=2. 2Hz), 8. 08 (1H, d, J=8. 6Hz), 7. 86~7. 83 (1H, m), 7. 77~7. 74 (1H, m), 7. 55 (1H, d, J=2. 2Hz), 7. 28 (1H, dd, J=7. 8, 4. 9Hz), 5. 03 (2H, s), 4. 13 (2H, t, J=6. 4Hz), 3. 89 (2H, s), 1. 60~1. 50 (2H, m), 1. 19~1. 16 (4H, m), 0. 72 (3H, t, J=6. 8Hz)	129. 8-133. 3
15	2939, 1751, 1601, 1581, 1473, 1340, 1192	*DMSO-d6:9. 16 (1H, s), 8. 63 (1H, s), 8. 60~8. 59 (1H, m), 8. 39~8. 37 (1H, m), 8. 35~8. 34 (1H, m), 8. 08 (1H, d, J=8. 6Hz), 7. 86~7. 83 (1H, m), 7. 77~7. 75 (1H, m), 7. 55~7. 52 (1H, m), 7. 31~7. 25 (1H, m), 5. 00 (2H, s), 4. 80~4. 75 (1H, m), 3. 90 (2H, s), 1. 77~1. 75 (2H, m), 1. 67~1. 55 (2H, m), 1. 44~1. 17 (6H, m)	142. 4-145. 5
16	2920, 1751, 1605, 1578, 1504, 1327, 716	*DMSO-d6:9. 13 (1H, s), 8. 61 (1H, s), 8. 56~8. 54 (1H, m), 8. 40~8. 29 (2H, m), 8. 05 (1H, d, J=8. 6Hz), 7. 85~7. 60 (2H, m), 7. 53 (1H, d, J=2. 2Hz), 7. 25 (1H, dd, J=8. 1, 4. 6Hz), 5. 01 (2H, s), 4. 23 (2H, t, J=5. 8Hz), 3. 88 (2H, s), 2. 58~2. 48 (2H, m), 2. 17 (6H, s)	74. 8-78. 8

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
17	1718, 1603, 1504, 1327, 798	*DMSO-d6: 12. 30 (1H, bs), 9. 17 (1H, s), 8. 63 (1H, d, J=2. 0Hz), 8. 63 (1H, d, J=1. 6Hz), 8. 41 (1H, d, J=2. 2Hz), 8. 38 (1H, dd, J=4. 6, 1. 6Hz), 8. 08 (1H, d, J=8. 7Hz), 7. 85 (1H, dd, J=8. 7, 2. 0Hz), 7. 78~7. 74 (1H, m), 7. 67 (1H, d, J=2. 2Hz), 7. 30~7. 26 (1H, m), 6. 87 (1H, d, J=6. 2Hz), 5. 18~5. 10 (1H, m), 3. 90 (2H, s), 3. 22 (2H, dd, J=7. 1, 1. 6Hz)	161. 5-164. 9
18	3402, 1647, 1591, 1576, 1506, 1471, 1331, 712	*DMSO-d6: 9. 13 (1H, s), 8. 75 (1H, d, J=1. 6Hz), 8. 63 (1H, d, J=1. 6Hz), 8. 57 (1H, dd, J=4. 9, 1. 6Hz), 8. 55 (1H, d, J=1. 9Hz), 8. 38 (1H, dd, J=4. 9, 1. 6Hz), 8. 36 (1H, d, J=2. 2Hz), 8. 06 (1H, d, J=8. 9Hz), 7. 96~7. 94 (1H, m), 7. 83 (1H, dd, J=8. 9, 1. 9Hz), 7. 78~7. 74 (1H, m), 7. 70 (1H, d, J=2. 2Hz), 7. 46 (1H, dd, J=7. 9, 4. 9Hz), 7. 28 (1H, dd, J=7. 9, 4. 9Hz), 5. 36 (2H, s), 3. 89 (2H, s)	181. 0-183. 2
19	3000, 1601, 1579, 1502, 1331, 1232, 797	*DMSO-d6: 9. 12 (1H, s), 8. 65~8. 57 (3H, m), 8. 54 (1H, d, J=1. 8Hz), 8. 41~8. 36 (2H, m), 8. 05 (1H, d, J=8. 7Hz), 7. 81 (1H, dd, J=8. 7, 1. 8Hz), 7. 77~7. 74 (1H, m), 7. 65~7. 64 (1H, m), 7. 54~7. 50 (2H, m), 7. 30~7. 25 (1H, m), 5. 39 (2H, s), 3. 88 (2H, s)	239. 0 (decomposition)
20	3000, 1593, 1578, 1504, 1473, 1327	*DMSO-d6: 9. 14 (1H, s), 8. 63~8. 57 (3H, m), 8. 40~8. 36 (2H, m), 8. 07 (1H, d, J=8. 9Hz), 7. 86~7. 81 (2H, m), 7. 76 (1H, d, J=7. 9Hz), 7. 66 (1H, d, J=2. 3Hz), 7. 59 (1H, d, J=7. 6Hz), 7. 42~7. 32 (1H, m), 7. 30~7. 27 (1H, m), 5. 39 (2H, s), 3. 89 (2H, s)	193. 4 (decomposition)
21	3450, 1740, 1647, 1608, 1504, 1277, 733	*DMSO-d6: 9. 32 (1H, d, J=1. 6Hz), 9. 17 (1H, s), 8. 92 (1H, dd, J=4. 9, 1. 6Hz), 8. 63 (1H, d, J=1. 8Hz), 8. 57~8. 50 (2H, m), 8. 49 (1H, d, J=1. 6Hz), 8. 37 (1H, m), 8. 09~8. 04 (2H, m), 7. 83 (1H, dd, J=8. 7, 1. 8Hz), 7. 76 (1H, d, J=8. 0Hz), 7. 68 (1H, dd, J=8. 1, 4. 9Hz), 7. 27 (1H, dd, J=8. 0, 4. 9Hz), 3. 89 (2H, s)	153. 6-160. 9

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
22	1603, 1578, 1502, 1329, 729	DMSO-d6: 9.13 (1H, s), 8.63 (1H, d, J=1.8 Hz), 8.55 (1H, d, J=2.0Hz), 8.38 (1H, dd, J=4.6, 1.8Hz), 8.35 (1H, d, J=2.0Hz), 8.06 (1H, d, J=8.8Hz), 7.82 (1H, dd, J=8.8, 2.0 Hz), 7.76 (1H, d, J=7.8Hz), 7.66 (1H, d, J=2.0Hz), 7.54～7.51 (2H, m), 7.45～7.32 (3H, m), 7.23 (1H, dd, J=7.8, 4.6Hz), 5.31 (2H, s), 3.89 (2H, s)	181.6-185.0
23	1687, 1597, 1578, 1506, 1329, 1230, 970	*DMSO-d6: 9.15 (1H, s), 8.62 (1H, d, J=1.9Hz), 8.59 (1H, d, J=1.9Hz), 8.38～8.36 (2H, m), 8.09～8.06 (3H, m), 7.83 (1H, dd, J=8.7, 1.9Hz), 7.77～7.70 (2H, m), 7.63～7.58 (3H, m), 7.29～7.25 (1H, m), 5.84 (2H, s), 3.89 (2H, s)	241.9 (decomposition)
24	1728, 1603, 1504, 1331, 1248, 1232	*DMSO-d6: 9.14 (1H, s), 8.72 (1H, bs), 8.64 (1H, s), 8.59 (1H, s), 8.55 (1H, d, J=1.9 Hz), 8.39～8.36 (2H, m), 8.10～7.94 (2H, m), 7.87～7.73 (2H, m), 7.71 (1H, d, J=2.2 Hz), 7.31～7.25 (1H, m), 5.38 (2H, s), 5.16 (2H, s), 3.90 (2H, s), 2.07 (3H, s)	140.6-144.1
25	1599, 1578, 1506, 1327, 1028, 714	*DMSO-d6: 9.15 (1H, s), 8.64～8.60 (2H, m), 8.56 (1H, d, J=1.9Hz), 8.51 (1H, d, J=1.4Hz), 8.38～8.37 (2H, m), 8.07 (1H, d, J=8.7Hz), 7.92～7.86 (1H, m), 7.83 (1H, dd, J=8.7, 1.9Hz), 7.75 (1H, dd, J=7.9, 1.6Hz), 7.70 (1H, d, J=2.2Hz), 7.32～7.25 (1H, m), 5.37 (2H, s), 4.57 (2H, s), 3.90 (2H, s)	186.3-191.4
26	3500, 3000, 1601, 1579, 1504, 1329	*DMSO-d6: 9.12 (1H, s), 8.63 (1H, d, J=1.9Hz), 8.55 (1H, d, J=1.6Hz), 8.39～8.37 (1H, m), 8.26 (1H, d, J=2.2Hz), 8.05 (1H, d, J=9.7Hz), 7.83～7.75 (2H, m), 7.55 (1H, d, J=2.2Hz), 7.30～7.26 (1H, m), 4.62 (1H, t, J=5.4Hz), 4.22 (2H, t, J=6.4Hz), 3.89 (2H, s), 3.63～3.59 (2H, m), 1.99～1.92 (2H, m)	213.4-220.8

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
27	3500, 3000, 1597, 1500, 1329, 1227	*DMSO-d6: 9. 11 (1H, s), 8. 68～8. 60 (1H, m), 8. 54 (1H, d, J=1. 6Hz), 8. 45～8. 35 (1H, m), 8. 24 (1H, d, J=2. 2Hz), 8. 04 (1H, d, J=8. 7Hz), 7. 88～7. 76 (2H, m), 7. 54 (1H, d, J=2. 2Hz), 7. 31～7. 27 (1H, m), 4. 52～4. 48 (1H, m), 4. 16 (2H, t, J=6. 5Hz), 3. 89 (2H, s), 3. 51～3. 47 (2H, m), 1. 86～1. 81 (2H, m), 1. 67～1. 60 (2H, m)	161. 7-166. 6
28	3500, 3000, 1593, 1578, 1506, 1335, 764	*DMSO-d6: 9. 13 (1H, s), 8. 63 (1H, d, J=1. 9Hz), 8. 56 (1H, d, J=1. 9Hz), 8. 39～8. 37 (1H, m), 8. 27 (1H, d, J=2. 3Hz), 8. 06 (1H, d, J=8. 6Hz), 7. 82 (1H, dd, J=8. 6, 1. 9Hz), 7. 78～7. 75 (1H, m), 7. 56 (1H, d, J=2. 3Hz), 7. 30～7. 25 (1H, m), 4. 40 (1H, bs), 4. 15 (2H, t, J=6. 5Hz), 3. 89 (2H, s), 3. 45～3. 43 (2H, m), 1. 85～1. 75 (2H, m), 1. 53～1. 50 (4H, m)	186. 7-189. 4
29	2935, 2927, 1589, 1578, 1508, 1331, 1228	*DMSO-d6: 9. 08 (1H, s), 8. 61 (1H, d, J=1. 9Hz), 8. 51 (1H, d, J=1. 9Hz), 8. 37～8. 35 (1H, m), 8. 21 (1H, d, J=2. 2Hz), 8. 01 (1H, d, J=8. 7Hz), 7. 80～7. 73 (2H, m), 7. 50 (1H, d, J=2. 2Hz), 7. 28～7. 26 (1H, m), 4. 37 (1H, t, J=5. 2Hz), 4. 11 (2H, t, J=6. 5Hz), 3. 87 (2H, s), 3. 40～3. 38 (2H, m), 1. 78～1. 76 (2H, m), 1. 47～1. 38 (6H, m)	175. 1-178. 4
30	3433, 1591, 1572, 1508, 1327, 1115, 714	*DMSO-d6: 9. 11 (1H, s), 8. 65～8. 62 (1H, m), 8. 53 (1H, d, J=1. 9Hz), 8. 39～8. 37 (1H, m), 8. 26 (1H, d, J=2. 3Hz), 8. 05 (1H, d, J=8. 7Hz), 7. 83～7. 75 (2H, m), 7. 56 (1H, d, J=2. 3Hz), 7. 28 (1H, dd, J=7. 9, 4. 9Hz), 4. 69～4. 66 (1H, m), 4. 29～4. 26 (2H, m), 3. 89 (2H, s), 3. 85～3. 82 (2H, m), 3. 57～3. 52 (4H, m)	123. 9-128. 9
31	2927, 1647, 1605, 1578, 1508, 1329, 797	DMSO-d6: 9. 12 (1H, s), 8. 63 (1H, s), 8. 58 (1H, d, J=1. 7Hz), 8. 40～8. 35 (1H, m), 8. 29 (1H, d, J=2. 0Hz), 8. 06 (1H, d, J=8. 9Hz), 7. 84～7. 75 (2H, m), 7. 56 (1H, d, J=2. 0Hz), 7. 30～7. 26 (1H, m), 4. 71～4. 67 (1H, m), 3. 95～3. 80 (4H, m), 3. 47～3. 30 (2H, m), 1. 07 (6H, s)	112. 7-113. 9

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
32	1716, 1564, 1508, 1327, 1049, 716	*DMSO-d6: 9. 16 (1H, s), 8. 63 (1H, s), 8. 57 (1H, s), 8. 39~8. 27 (2H, m), 8. 08 (1H, d, J=8. 4Hz), 7. 86~7. 74 (2H, m), 7. 54 (1H, d, J=1. 6Hz), 7. 28 (1H, dd, J=7. 6, 4. 6Hz), 5. 09 (2H, s), 4. 80 (1H, t, J=4. 9Hz), 3. 89 (2H, s), 3. 75~3. 69 (2H, m), 2. 72~2. 68 (2H, m)	211. 7-214. 7
33	3500, 3000, 1603, 1578, 1504, 1468, 1331	*DMSO-d6: 9. 14 (1H, s), 8. 63 (1H, d, J=1. 9Hz), 8. 56 (1H, s), 8. 39~8. 37 (1H, m), 8. 26 (1H, d, J=1. 6Hz), 8. 07 (1H, d, J=8. 7Hz), 7. 84~7. 74 (2H, m), 7. 55 (1H, d, J=1. 6Hz), 7. 28 (1H, dd, J=7. 9, 4. 9Hz), 4. 21 (2H, q, J=7. 0Hz), 3. 89 (2H, s), 1. 42 (3H, t, J=7. 0Hz)	180. 3-182. 8
34	3000, 1603, 1578, 1504, 1466, 1329	DMSO-d6: 9. 08 (1H, s), 8. 63 (1H, d, J=1. 5Hz), 8. 51 (1H, d, J=1. 5Hz), 8. 38 (1H, dd, J=4. 4, 1. 5Hz), 8. 21 (1H, d, J=2. 0Hz), 8. 02 (1H, d, J=8. 8Hz), 7. 81~7. 74 (2H, m), 7. 51 (1H, d, J=2. 0Hz), 7. 28 (1H, dd, J=7. 8, 4. 4Hz), 4. 15~4. 10 (2H, m), 3. 88 (2H, s), 1. 81~1. 73 (2H. m), 1. 54~1. 45 (2H. m), 0. 97 (3H, t, J=7. 3Hz)	168. 1-176. 2
35	3100, 1649, 1603, 1578, 1504, 1328, 1115, 797	DMSO-d6: 9. 09 (1H, s), 8. 63 (1H, d, J=1. 5Hz), 8. 51 (1H, d, J=2. 0Hz), 8. 39~8. 37 (1H, m), 8. 23 (1H, d, J=1. 9Hz), 8. 03 (1H, d, J=8. 8Hz), 7. 82~7. 75 (2H. m), 7. 55 (1H, d, J=1. 9Hz), 7. 29 (1H, dd, J=7. 6, 4. 6Hz), 4. 27 (2H, t, J=4. 4Hz), 3. 89 (2H, s), 3. 75 (2H, t, J=4. 4Hz), 3. 35 (3H, s)	155. 0-159. 7
36	1595, 1579, 1506, 1470, 1335, 1230, 1119	*DMSO-d6: 9. 10 (1H, s), 8. 62 (1H, s), 8. 52 (1H, d, J=1. 9Hz), 8. 38~8. 34 (1H, m), 8. 25 (1H, d, J=2. 3Hz), 8. 03 (1H, d, J=8. 7Hz), 7. 82~7. 75 (2H, m), 7. 55 (1H, d, J=2. 3Hz), 7. 28 (1H, dd, J=7. 7, 4. 7Hz), 4. 25 (2H, m), 3. 88 (2H, s), 3. 77 (2H, m), 3. 53 (2H, q, J=7. 1Hz), 1. 14 (3H, t, J=7. 1Hz)	174. 9-177. 0
37	2972, 1649, 1599, 1578, 1508, 1335, 800, 712	*DMSO-d6: 9. 15 (1H, s), 8. 63 (1H, d, J=2. 2Hz), 8. 58 (1H, d, J=1. 9Hz), 8. 40~8. 36 (1H, m), 8. 34 (1H, d, J=2. 3Hz), 8. 07 (1H, d, J=8. 7Hz), 7. 83 (1H, dd, J=8. 7, 1. 9Hz), 7. 79~7. 74 (1H, m), 7. 59 (1H, d, J=2. 3Hz), 7. 30~7. 26 (1H, m), 4. 90 (1H, t, J=5. 2Hz), 4. 15 (2H, d, J=5. 2Hz), 3. 89 (2H, s), 3. 78~3. 55 (4H, m), 1. 19~1. 14 (6H, m)	150. 2-154. 1

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
38	1761, 1605, 1578, 1500, 1329, 1211	DMSO-d6: 9. 22 (1H, s), 8. 64 (1H, s), 8. 59 (1H, s), 8. 42～8. 38 (2H, m), 8. 12 (1H, d, J=8. 8Hz), 7. 88～7. 86 (2H, m), 7. 78～7. 75 (1H, m), 7. 31～7. 26 (1H, m), 3. 91 (2H, s), 2. 38 (3H, s)	127. 7-134. 0
39	2950, 1724, 1599, 1578, 1506, 1327, 798	*DMSO-d6: 9. 10 (1H, s), 8. 63 (1H, s), 8. 53 (1H, s), 8. 38 (1H, d, J=4. 2Hz), 8. 23 (1H, d, J=2. 0Hz), 8. 03 (1H, d, J=8. 7Hz), 7. 82～7. 74 (2H, m), 7. 49 (1H, d, J=2. 0Hz), 7. 28 (1H, dd, J=7. 8, 4. 2Hz), 5. 05 (2H, s), 3. 88 (2H, s), 2. 60 (2H, q, J=7. 5Hz), 1. 01 (3H, t, J=7. 5Hz)	204. 5 (decomposition)
40	1718, 1599, 1578, 1506, 1329	*DMSO-d6: 9. 15 (1H, s), 8. 63 (1H, d, J=1. 4Hz), 8. 58 (1H, d, J=1. 9Hz), 8. 38 (1H, dd, J=4. 9, 1. 4Hz), 8. 28 (1H, d, J=2. 3Hz), 8. 07 (1H, d, J=8. 8Hz), 7. 83 (1H, dd, J=8. 8, 1. 9Hz), 7. 74～7. 70 (1H, m), 7. 51 (1H, d, J=2. 3Hz), 7. 28 (1H, dd, J=7. 6, 4. 9Hz), 5. 06 (2H, s), 3. 89 (2H, s), 2. 58～2. 53 (2H, m), 1. 60～1. 53 (2H, m), 0. 90 (3H, t, J=7. 3Hz)	212. 6 (decomposition)
41	3435, 2951, 1599, 1578, 1508, 1331	*DMSO-d6: 9. 13 (1H, s), 8. 63 (1H, s), 8. 58～8. 57 (1H, m), 8. 39～8. 37 (1H, m), 8. 29～8. 27 (1H, m), 8. 06 (1H, d, J=8. 6Hz), 7. 83～7. 80 (1H, m), 7. 76 (1H, d, J=7. 9Hz), 7. 58～7. 55 (1H, m), 7. 30～7. 26 (1H, m), 4. 94 (1H, d, J=5. 1Hz), 4. 02～4. 00 (2H, m), 3. 94～3. 82 (3H, m), 1. 51～1. 47 (4H, m), 0. 94～0. 90 (3H, m)	180. 0-184. 9
42	3431, 1713, 1601, 1578, 1504, 1473, 1325	*DMSO-d6: 9. 12 (1H, s), 8. 61 (1H, s), 8. 55 (1H, d, J=1. 9Hz), 8. 43～8. 31 (1H, m), 8. 25 (1H, d, J=2. 4Hz), 8. 05 (1H, d, J=8. 7Hz), 7. 83～7. 73 (2H, m), 7. 49 (1H, d, J=2. 4Hz), 7. 26 (1H, dd, J=7. 6, 4. 6Hz), 5. 33 (2H, s), 3. 87 (2H, s), 1. 20 (9H, s)	238. 7-240. 0
43	3400, 3000, 1662, 1576, 1506, 1325	*DMSO-d6: 9. 10 (1H, s), 8. 61～8. 60 (1H, m), 8. 52 (1H, d, J=1. 6Hz), 8. 37～8. 35 (1H m), 8. 28～8. 23 (2H, m), 8. 03 (1H, d, J=8. 7Hz), 7. 81～7. 73 (2H, m), 7. 59 (1H, d, J=2. 2Hz), 7. 26 (1H, dd, J=7. 6, 4. 9Hz), 4. 64 (2H, s), 3. 87 (2H, s), 3. 21～3. 12 (2H, m), 1. 04 (3H, t, J=7. 2Hz)	309. 8 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
44	3435, 1660, 1649, 1576, 1506, 1327, 1117, 795	*DMSO-d6: 9. 11 (1H, s), 8. 61 (1H, d, J=2. 5Hz), 8. 54 (1H, d, J=1. 5Hz), 8. 36 (1H, dd, J=4. 7, 1. 5Hz), 8. 25 (1H, d, J=2. 2Hz), 8. 04 (1H, d, J=8. 7Hz), 7. 81～7. 72 (2H, m), 7. 56 (1H, d, J=2. 2Hz), 7. 26 (1H, dd, J=7. 7, 4. 7Hz), 5. 06 (2H, s), 3. 87 (2H, s), 3. 64～3. 45 (8H, m)	150. 2-153. 1
45	2930, 1726, 1653, 1603, 1327, 1180, 1039	*DMSO-d6: 9. 15 (1H, s), 8. 62 (1H, s), 8. 58 (1H, d, J=1. 9Hz), 8. 39～8. 37 (1H, m), 8. 28 (1H, d, J=2. 2Hz), 8. 07 (1H, d, J=8. 7Hz), 7. 83 (1H, dd, J=8. 7, 1. 9Hz), 7. 78～7. 73 (1H, m), 7. 57 (1H, d, J=2. 2Hz), 7. 32～7. 25 (1H, m), 5. 06 (2H, m), 4. 24～4. 03 (3H, m), 3. 92～3. 83 (3H, m), 3. 26～3. 08 (1H, m), 2. 88～2. 58 (2H, m), 1. 97～1. 81 (2H, m), 1. 72～1. 55 (1H, m), 1. 49～1. 34 (1H, m), 1. 19 (3H, t, J=7. 1Hz)	107. 0-114. 5
46	1718, 1653, 1560, 1508, 1323, 1205	*DMSO-d6: 12. 32 (1H, bs), 9. 15 (1H, s), 8. 63 (1H, d, J=1. 6Hz), 8. 58 (1H, d, J=1. 9Hz), 8. 38～8. 37 (1H, m), 8. 28 (1H, d, J=2. 3Hz), 8. 07 (1H, d, J=8. 7Hz), 7. 83 (1H, dd, J=8. 7, 1. 9Hz), 7. 81～7. 74 (1H, m), 7. 57 (1H, d, J=2. 3Hz), 7. 30～7. 25 (1H, m), 5. 06 (2H, s), 4. 23～4. 13 (1H, m), 3. 95～3. 79 (3H, m), 3. 25～3. 10 (1H, m), 2. 88～2. 71 (1H, m), 2. 55～2. 54 (1H, m), 1. 96～1. 79 (2H, m), 1. 70～1. 53 (1H, m), 1. 49～1. 32 (1H, m)	156. 0-164. 4
47	3365, 1676, 1643, 1601, 1506, 1327, 797	*DMSO-d6: 9. 14 (1H, s), 8. 89～8. 81 (1H, m), 8. 63 (1H, s), 8. 56 (1H, d, J=1. 9Hz), 8. 41～8. 36 (1H, m), 8. 32 (1H, d, J=2. 2Hz), 8. 07 (1H, d, J=8. 5Hz), 7. 83 (1H, dd, J=8. 5, 1. 9Hz), 7. 76 (1H, d, J=7. 8Hz), 7. 63 (1H, d, J=2. 2Hz), 7. 28 (1H, dd, J=7. 8, 4. 7Hz), 5. 72～5. 68 (1H, m), 4. 71 (2H, s), 4. 62～4. 58 (2H, m), 3. 89 (2H, s)	217. 9-221. 6
48	3055, 1647, 1597, 1581, 1508, 1477, 1331	DMSO-d6: 8. 94 (1H, s), 8. 58～8. 50 (1H, m), 8. 26 (1H, d, J=1. 8Hz), 8. 05 (1H, d, J=8. 8Hz), 7. 80 (1H, dd, J=8. 8, 2. 0Hz), 7. 60 (1H, d, J=1. 8Hz), 3. 96 (3H, s), 2. 12 (3H, s)	301. 1 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
49	3115, 1560, 1446, 1327, 1282, 1159	*DMSO-d6:8. 91 (1H, s), 8. 52 (1H, d, J=2. 0Hz), 8. 05~7. 99 (2H, m), 7. 77 (1H, dd, J=8. 7, 2. 0Hz), 7. 52 (1H, d, J=2. 2Hz), 2. 10 (3H, s)	325. 2 (decomposition)
50	3498, 3000, 1745, 1647, 1601, 1329, 1145, 849	*DMSO-d6:8. 96 (1H, s), 8. 58 (1H, d, J=2. 0Hz), 8. 30 (1H, d, J=2. 3Hz), 8. 07 (1H, d, J=8. 6Hz), 7. 81 (1H, dd, J=8. 6, 2. 0Hz), 7. 55 (1H, d, J=2. 3Hz), 4. 89 (2H, s), 2. 11 (3H, s), 1. 45 (9H, s)	196. 4-198. 1
51	3500, 3000, 1747, 1601, 1504, 1232	*DMSO-d6:8. 96 (1H, s), 8. 58 (1H, d, J=1. 9Hz), 8. 32 (1H, d, J=2. 3Hz), 8. 07 (1H, d, J=8. 7Hz), 7. 82 (1H, dd, J=8. 7, 1. 9Hz), 7. 57 (1H, d, J=2. 3Hz), 5. 05~4. 98 (3H, m), 2. 12 (3H, s), 1. 24~1. 22 (6H, m)	184. 1-187. 4
52	3000, 1751, 1599, 1504, 1338, 1188	DMSO-d6:8. 92 (1H, s), 8. 54 (1H, s), 8. 28 (1H, d, J=1. 5Hz), 8. 03 (1H, d, J=8. 8Hz), 7. 78 (1H, d, J=8. 8Hz), 7. 56 (1H, d, J=1. 5Hz), 5. 00 (2H, s), 4. 21 (2H, q, J=7. 0Hz), 2. 11 (3H, s), 1. 24 (3H, t, J=7. 0Hz)	188. 6 (decomposition)
53	3500, 1749, 1560, 1506, 1327, 1188, 1159	DMSO-d6:8. 92 (1H, s), 8. 55 (1H, d, J=2. 0Hz), 8. 27 (1H, d, J=2. 4Hz), 8. 03 (1H, d, J=8. 8Hz), 7. 79 (1H, dd, J=8. 8, 2. 0Hz), 7. 53 (1H, d, J=2. 4Hz), 4. 91 (2H, s), 2. 11 (3H, s)	304. 0 (decomposition)
54	3000, 1601, 1579, 1502, 1325, 1286	*DMSO-d6:8. 91 (1H, s), 8. 77 (1H, d, J=1. 1Hz), 8. 59~8. 57 (1H, m), 8. 51 (1H, d, J=1. 3Hz), 8. 32 (1H, d, J=2. 0Hz), 8. 05~7. 95 (2H, m), 7. 79 (1H, dd, J=8. 4, 1. 3Hz), 7. 70 (1H, d, J=2. 0Hz), 7. 47 (1H, dd, J=7. 9, 4. 9Hz), 5. 36 (2H, s), 2. 09 (3H, s)	248. 0 (decomposition)
55	1601, 1579, 1504, 1325, 1047	*DMSO-d6:8. 95 (1H, s), 8. 56~8. 55 (1H, m), 8. 27 (1H, d, J=2. 0Hz), 8. 06 (1H, d, J=8. 7Hz), 7. 82~7. 79 (1H, m), 7. 59 (1H, d, J=2. 0Hz), 4. 50 (1H, d, J=5. 2Hz), 4. 18 (2H, t, J=6. 5Hz), 3. 53~3. 47 (2H, m), 2. 12 (3H, s), 1. 92~1. 79 (2H, m), 1. 69~1. 57 (2H, m)	106. 7-109. 5
56	1757, 1605, 1504, 1331, 1217, 1200	DMSO-d6:9. 04 (1H, s), 8. 60~8. 56 (1H, m), 8. 41 (1H, d, J=2. 0Hz), 8. 11 (1H, d, J=8. 3Hz), 7. 91 (1H, d, J=2. 0Hz), 7. 87~7. 84 (1H, m), 2. 38 (3H, s), 2. 13 (3H, s)	331. 3 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
57	3000, 1732, 1578, 1508, 1325	*DMSO-d6: 8. 92 (1H, s), 8. 54 (1H, d, J=1. 9Hz), 8. 24 (1H, d, J=2. 3Hz), 8. 03 (1H, d, J=8. 7Hz), 7. 79 (1H, dd, J=8. 7, 1. 9Hz), 7. 52 (1H, d, J=2. 3Hz), 5. 05 (2H, s), 2. 58~2. 53 (2H, m), 2. 09 (3H, s), 1. 60~1. 53 (2H, m), 0. 89 (3H, t, J=7. 3Hz)	208. 2-211. 9
58	1651, 1608, 1498, 1325, 816, 731	*DMSO-d6: 8. 90 (1H, d, J=7. 7Hz), 8. 54 (1H, d, J=2. 0Hz), 8. 24 (1H, d, J=2. 2Hz), 8. 07 (1H, d, J=8. 7Hz), 7. 79 (1H, dd, J=8. 7, 2. 0Hz), 7. 55 (1H, d, J=2. 2Hz), 6. 35 (1H, d, J=7. 7Hz), 3. 94 (3H, s)	250. 2-254. 5
59	3000, 1649, 1599, 1500, 1423, 1184, 829	*DMSO-d6: 10. 18 (1H, s), 8. 90 (1H, d, J=7. 6Hz), 8. 54 (1H, d, J=2. 0Hz), 8. 08 (1H, d, J=8. 7Hz), 8. 02 (1H, d, J=2. 2Hz), 7. 78 (1H, dd, J=8. 7, 2. 0Hz), 7. 49 (1H, d, J=2. 2Hz), 6. 33 (1H, d, J=7. 6Hz)	360. 0<
60	3020, 1757, 1641, 1500, 1321, 1254, 814	*DMSO-d6: 8. 94 (1H, d, J=7. 6Hz), 8. 58 (1H, d, J=2. 1Hz), 8. 31 (1H, d, J=2. 4Hz), 8. 10 (1H, d, J=8. 7Hz), 7. 82 (1H, dd, J=8. 7, 2. 1Hz), 7. 52 (1H, d, J=2. 4Hz), 6. 37 (1H, d, J=7. 6Hz), 4. 89 (2H, s), 1. 49 (9H, s)	209. 2-211. 8
61	3000, 1757, 1605, 1500, 1321, 1198, 814	*DMSO-d6: 8. 95 (1H, d, J=7. 7Hz), 8. 59 (1H, d, J=1. 9Hz), 8. 34 (1H, d, J=2. 3Hz), 8. 12 (1H, d, J=8. 6Hz), 7. 83 (1H, dd, J=8. 6, 1. 9Hz), 7. 54 (1H, d, J=2. 3Hz), 6. 38 (1H, d, J=7. 7Hz), 5. 07~4. 99 (3H, m), 1. 26~1. 22 (6H, m)	190. 6-192. 6
62	3100, 1755, 1606, 1500, 1321, 1194, 816	DMSO-d6: 8. 94 (1H, d, J=7. 8Hz), 8. 58 (1H, d, J=2. 0Hz), 8. 33 (1H, d, J=2. 4Hz), 8. 11 (1H, d, J=8. 8Hz), 7. 82 (1H, dd, J=8. 8, 2. 0Hz), 7. 55 (1H, d, J=2. 4Hz), 6. 38 (1H, d, J=7. 8Hz), 5. 03 (2H, s), 4. 21 (2H, q, J=7. 1Hz), 1. 23 (3H, t, J=7. 1Hz)	189. 8 (decomposition)
63	3500, 1755, 1570, 1508, 1466, 1200, 822	DMSO-d6: 13. 13 (1H, bs), 8. 94 (1H, d, J=7. 6Hz), 8. 60 (1H, d, J=2. 0Hz), 8. 32 (1H, d, J=2. 4Hz), 8. 11 (1H, d, J=8. 5Hz), 7. 82 (1H, dd, J=8. 5, 2. 0Hz), 7. 53 (1H, d, J=2. 4Hz), 6. 38 (1H, d, J=7. 6Hz), 4. 92 (2H, s)	300. 0<

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
64	1649, 1612, 1500, 1317, 816	*DMSO-d6: 8. 93 (1H, d, J=7. 7Hz), 8. 77 (1H, d, J=1. 9Hz), 8. 59~8. 57 (1H, m), 8. 54 (1H, d, J=1. 9Hz), 8. 35 (1H, d, J=2. 2Hz), 8. 10 (1H, d, J=8. 8Hz), 7. 99~7. 95 (1H, m), 7. 81 (1H, dd, J=8. 8, 1. 9Hz), 7. 70 (1H, d, J=2. 2Hz), 7. 47 (1H, dd, J=7. 9, 4. 9Hz), 6. 37 (1H, d, J=7. 7Hz), 5. 38 (2H, s)	229. 3-233. 5
65	3000, 1649, 1616, 1504, 1387, 1192, 812	*DMSO-d6: 8. 93 (1H, d, J=7. 7Hz), 8. 63~8. 61 (1H, m), 8. 56 (1H, d, J=1. 9Hz), 8. 40 (1H, d, J=2. 3Hz), 8. 10 (1H, d, J=8. 7Hz), 7. 90~7. 79 (2H, m), 7. 66 (1H, d, J=2. 3Hz), 7. 62~7. 60 (1H, m), 7. 40~7. 36 (1H, m), 6. 37 (1H, d, J=7. 7Hz), 5. 40 (2H, s)	260. 9-263. 1
66	1649, 1614, 1500, 1323, 1186, 816	DMSO-d6: 8. 93 (1H, d, J=7. 3Hz), 8. 55 (1H, d, J=2. 1Hz), 8. 36 (1H, d, J=2. 2Hz), 8. 10 (1H, d, J=8. 5Hz), 7. 80 (1H, dd, J=8. 5, 2. 1Hz), 7. 67 (1H, d, J=2. 2Hz), 7. 56~7. 46 (2H, m), 7. 43~7. 37 (3H, m), 6. 37 (1H, d, J=7. 3Hz), 5. 32 (2H, s)	203. 2 (decomposition)
67	1650, 1606, 1502, 1323, 1190, 818	*DMSO-d6: 8. 93 (1H, d, J=7. 6Hz), 8. 57~8. 53 (2H, m), 8. 28 (1H, d, J=2. 0Hz), 8. 10 (1H, d, J=8. 7Hz), 7. 82~7. 73 (2H, m), 7. 58 (1H, d, J=2. 0Hz), 7. 43 (1H, d, J=8. 1Hz), 7. 29~7. 25 (1H, m), 6. 37 (1H, d, J=7. 6Hz), 4. 57 (2H, t, J=6. 5Hz), 3. 30 (2H, t, J=6. 5Hz)	117. 5-121. 5
68	3000, 1649, 1601, 1506, 1327, 1194, 825	*DMSO-d6: 8. 94 (1H, d, J=7. 7Hz), 8. 57 (1H, d, J=1. 9Hz), 8. 51~8. 50 (1H, m), 8. 42 (1H, dd, J=4. 6, 1. 4Hz), 8. 30 (1H, d, J=2. 2Hz), 8. 11 (1H, d, J=8. 7Hz), 7. 81 (1H, dd, J=8. 7, 1. 9Hz), 7. 73~7. 70 (1H, m), 7. 57 (1H, d, J=2. 2Hz), 7. 33 (1H, dd, J=7. 9, 4. 6Hz), 6. 37 (1H, d, J=7. 7Hz), 4. 18 (2H, t, J=6. 2Hz), 2. 85 (2H, t, J=7. 3Hz), 2. 17~2. 12 (2H, m)	165. 8-168. 4
69	1743, 1595, 1508, 1244, 820	*DMSO-d6: 8. 95 (1H, d, J=7. 7Hz), 8. 74~8. 71 (1H, m), 8. 60~8. 54 (2H, m), 8. 38~8. 36 (1H, m), 8. 13~8. 07 (1H, m), 7. 97~7. 96 (1H, m), 7. 85~7. 80 (1H, m), 7. 72~7. 70 (1H, m), 6. 38 (1H, d, J=7. 7Hz), 5. 39 (2H, s), 5. 16 (2H, s), 2. 08 (3H, s)	181. 2-185. 4

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
70	3500, 1647, 1601, 1504, 1471, 1325, 822	*DMSO-d6: 8.96 (1H, d, J=7.7Hz), 8.64 (1H, s), 8.57 (1H, d, J=1.6Hz), 8.51 (1H, s), 8.39 (1H, d, J=2.2Hz), 8.12 (1H, d, J=8.7Hz), 7.90 (1H, s), 7.82 (1H, dd, J=8.7, 1.6Hz), 7.72 (1H, d, J=2.2Hz), 6.39 (1H, d, J=7.7Hz), 5.39 (2H, s), 4.58 (2H, s)	206.0-208.6
71	1736, 1645, 1612, 1321, 1273, 818, 785	*DMSO-d6: 8.94 (1H, d, J=7.6Hz), 8.56 (1H, d, J=1.9Hz), 8.41 (1H, d, J=2.2Hz), 8.11 (1H, d, J=8.7Hz), 7.90 (1H, dd, J=7.9, 7.6Hz), 7.81 (1H, dd, J=8.7, 1.9Hz), 7.67 (1H, d, J=2.2Hz), 7.56 (1H, d, J=7.9Hz), 7.40 (1H, d, J=7.6Hz), 6.37 (1H, d, J=7.6Hz), 5.39 (2H, s), 5.18 (2H, s), 2.14 (3H, s)	204.6-207.8
72	1643, 1606, 1556, 1506, 1319, 818	*DMSO-d6: 8.92 (1H, d, J=7.6Hz), 8.55 (1H, d, J=1.9Hz), 8.39 (1H, d, J=2.3Hz), 8.09 (1H, d, J=8.7Hz), 7.88~7.86 (1H, m), 7.81 (1H, dd, J=8.7, 1.9Hz), 7.65 (1H, d, J=2.3Hz), 7.46~7.43 (2H, m), 6.36 (1H, d, J=7.6Hz), 5.49 (1H, t, J=5.9Hz), 5.36 (2H, s), 4.61 (2H, d, J=5.9Hz)	244.0-247.2
73	1718, 1601, 1502, 812	*DMSO-d6: 9.13~9.12 (1H, m), 8.95 (1H, d, J=7.6Hz), 8.59 (1H, d, J=1.9Hz), 8.44 (1H, d, J=2.4Hz), 8.39~8.36 (1H, m), 8.12 (1H, d, J=8.7Hz), 7.83 (1H, dd, J=8.7, 1.9Hz), 7.77 (1H, d, J=8.7Hz), 7.68 (1H, d, J=2.4Hz), 6.38 (1H, d, J=7.6Hz), 5.52 (2H, s), 3.90 (3H, s)	257.7 (decomposition)
74	1645, 1608, 1591, 1504, 1325, 822	*DMSO-d6: 8.96 (1H, d, J=7.6Hz), 8.57~8.56 (2H, m), 8.42 (1H, s), 8.38 (1H, d, J=2.2Hz), 8.12 (1H, d, J=8.7Hz), 7.83 (1H, dd, J=8.7, 1.4Hz), 7.78 (1H, s), 7.71 (1H, d, J=2.2Hz), 6.39 (1H, d, J=7.6Hz), 5.35 (2H, s), 2.34 (3H, s)	242.0-246.2
75	1649, 1606, 1506, 1387, 1325, 1190, 822	*DMSO-d6: 8.96 (1H, d, J=7.6Hz), 8.92 (1H, s), 8.72 (1H, d, J=2.4Hz), 8.67 (1H, d, J=2.4Hz), 8.58 (1H, d, J=1.6Hz), 8.43 (1H, d, J=2.3Hz), 8.12 (1H, d, J=8.7Hz), 7.85~7.81 (1H, m), 7.74 (1H, d, J=2.3Hz), 6.39 (1H, d, J=7.6Hz), 5.50 (2H, s)	267.0 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
76	3076, 1653, 1614, 1506, 1470, 1194, 818	*DMSO-d6:9. 72 (1H, s), 8. 96 (1H, d, J=7. 7Hz), 8. 58~8. 57 (1H, m), 8. 40~8. 38 (1H, m), 8. 12 (1H, d, J=8. 6Hz), 7. 85~7. 82 (1H, m), 7. 76 (1H, m), 6. 40 (1H, d, J=7. 7Hz), 5. 59 (2H, s)	250. 0 (decomposition)
77	2933, 2781, 1649, 1610, 1504, 1325, 818	*DMSO-d6:8. 86 (1H, d, J=7. 9Hz), 8. 48 (1H, d, J=1. 9Hz), 8. 19 (1H, d, J=1. 9Hz), 8. 04 (1H, d, J=8. 7Hz), 7. 76 (1H, dd, J=8. 7, 1. 9Hz), 7. 50~7. 49 (1H, m), 6. 33 (1H, d, J=7. 9Hz), 4. 04~3. 95 (2H, m), 2. 92~2. 83 (1H, m), 2. 69~2. 58 (1H, m), 2. 18 (3H, s), 2. 13~2. 08 (1H, m), 1. 99~1. 45 (6H, m)	149. 3-154. 8
78	2765, 1647, 1608, 1504, 1464, 820	*DMSO-d6:8. 92 (1H, d, J=7. 7Hz), 8. 56 (1H, d, J=1. 9Hz), 8. 27 (1H, d, J=2. 3Hz), 8. 09 (1H, d, J=8. 7Hz), 7. 82~7. 78 (1H, m), 7. 55 (1H, d, J=2. 3Hz), 6. 36 (1H, d, J=7. 7Hz), 4. 19 (2H, t, J=6. 4Hz), 2. 46 (2H, t, J=7. 1Hz), 2. 20 (6H, s), 2. 00~1. 91 (2H, m)	128. 8-129. 2
79	1597, 1504, 1321, 1190, 820	*DMSO-d6:8. 93 (1H, d, J=7. 6Hz), 8. 56 (1H, d, J=1. 9Hz), 8. 28 (1H, d, J=2. 0Hz), 8. 10 (1H, d, J=8. 8Hz), 7. 81 (1H, dd, J=8. 8, 1. 9Hz), 7. 56 (1H, d, J=2. 0Hz), 6. 37 (1H, d, J=7. 6Hz), 4. 53~4. 49 (1H, m), 4. 18 (2H, t, J=6. 4Hz), 3. 51~3. 49 (2H, m), 1. 92~1. 78 (2H, m), 1. 70~1. 57 (2H, m)	89. 8-92. 9
80	3367, 2939, 2866, 1597, 1504, 1321, 1192	DMSO-d6:8. 85 (1H, d, J=7. 6Hz), 8. 47 (1H, d, J=1. 8Hz), 8. 16 (1H, d, J=2. 1Hz), 8. 03 (1H, d, J=8. 6Hz), 7. 75 (1H, dd, J=8. 6, 1. 8Hz), 7. 48 (1H, d, J=2. 1Hz), 6. 33 (1H, d, J=7. 6Hz), 4. 45~4. 42 (1H, m), 4. 15~4. 10 (2H, m), 3. 50~3. 40 (2H, m), 1. 84~1. 79 (2H, m), 1. 54~1. 51 (4H, m)	145. 3-150. 9
81	2935, 2927, 1589, 1502, 1323, 1190, 818	*DMSO-d6:8. 91 (1H, d, J=7. 9Hz), 8. 54 (1H, d, J=1. 9Hz), 8. 25 (1H, d, J=2. 2Hz), 8. 09 (1H, d, J=8. 7Hz), 7. 81 (1H, dd, J=8. 7, 1. 9Hz), 7. 54 (1H, d, J=2. 2Hz), 6. 36 (1H, d, J=7. 9Hz), 4. 39 (1H, t, J=5. 2Hz), 4. 15 (2H, t, J=6. 4Hz), 3. 43~3. 39 (2H, m), 1. 81~1. 79 (2H, m), 1. 51~1. 42 (6H, m)	106. 9-110. 8
82	1765, 1651, 1608, 1504, 1323, 1203, 820	DMSO-d6:9. 00 (1H, d, J=7. 8Hz), 8. 57 (1H, d, J=2. 0Hz), 8. 40 (1H, d, J=2. 0Hz), 8. 13 (1H, d, J=8. 3Hz), 7. 88~7. 83 (2H, m), 6. 43 (1H, d, J=7. 8Hz), 2. 39 (3H, s)	286. 2 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
83	3000, 1720, 1610, 1504, 1321, 822	*DMSO-d6: 8. 93 (1H, d, J=7. 7Hz), 8. 57 (1H, d, J=1. 8Hz), 8. 27 (1H, d, J=2. 3Hz), 8. 10 (1H, d, J=8. 7Hz), 7. 81 (1H, dd, J=8. 7, 1. 8Hz), 7. 51 (1H, d, J=2. 3Hz), 6. 36 (1H, d, J=7. 7Hz), 5. 06 (2H, s), 2. 55 (2H, t, J=7. 5Hz), 1. 60～1. 52 (2H, m), 0. 89 (3H, t, J=7. 5Hz)	199. 7-203. 5
84	1605, 1597, 1506, 1475, 1435, 1340	DMSO-d6: 9. 06 (1H, s), 8. 56 (1H, d, J=2. 0Hz), 8. 44 (1H, d, J=3. 9Hz), 8. 26 (1H, d, J=2. 2Hz), 8. 09 (1H, d, J=8. 8Hz), 7. 79 (1H, dd, J=8. 8, 2. 0Hz), 7. 70～7. 64 (1H, m), 7. 56 (1H, d, J=2. 2Hz), 7. 37 (1H, d, J=7. 8Hz), 7. 21～7. 16 (1H, m), 4. 04 (2H, s), 3. 94 (3H, s)	218. 9 (decomposition)
85	1605, 1498, 1394, 1338, 804	DMSO-d6: 10. 14 (1H, bs), 9. 03 (1H, s), 8. 53 (1H, d, J=2. 0Hz), 8. 44 (1H, d, J=4. 4Hz), 8. 08 (1H, d, J=8. 8Hz), 8. 01 (1H, d, J=2. 0Hz), 7. 77 (1H, dd, J=8. 8, 2. 0Hz), 7. 70～7. 64 (1H, m), 7. 49 (1H, d, J=2. 0Hz), 7. 36 (1H, d, J=7. 8Hz), 7. 21～7. 17 (1H, m), 4. 02 (2H, s)	329. 5 (decomposition)
86.	3003, 1743, 1734, 1603, 1502, 1153, 843	*DMSO-d6: 9. 10 (1H, s), 8. 61 (1H, d, J=1. 9Hz), 8. 47～8. 42 (1H, m), 8. 33 (1H, d, J=2. 3Hz), 8. 13 (1H, d, J=8. 7Hz), 7. 82 (1H, dd, J=8. 7, 1. 9Hz), 7. 70～7. 64 (1H, m), 7. 52 (1H, d, J=2. 3Hz), 7. 37 (1H, d, J=7. 6Hz), 7. 23～7. 15 (1H, m), 4. 88 (2H, s), 4. 04 (2H, s), 1. 44 (9H, s)	187. 4-188. 2
87	3000, 1599, 1578, 1473, 1325, 1282, 1153	DMSO-d6: 9. 11 (1H, s), 8. 55 (1H, d, J=2. 0Hz), 8. 45～8. 41 (2H, m), 8. 24 (1H, d, J=2. 4Hz), 8. 04 (1H, d, J=8. 8Hz), 7. 83～7. 79 (1H, m), 7. 55 (1H, d, J=2. 4Hz), 7. 37～7. 35 (2H, m), 3. 94 (3H, s), 3. 90 (2H, s)	225. 6-226. 5
88	1643, 1606, 1597, 1578, 1466, 1329, 1277, 798	*DMSO-d6: 10. 16 (1H, s), 9. 12 (1H, s), 8. 54 (1H, d, J=1. 9Hz), 8. 45～8. 41 (2H, m), 8. 02～8. 06 (2H, m), 7. 79 (1H, dd, J=8. 7, 1. 9Hz), 7. 49 (1H, d, J=1. 9Hz), 7. 35～7. 39 (2H, m), 3. 88 (2H, s)	301. 1 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
89	2978, 1751, 1603, 1504, 1327, 1153, 800	*DMSO-d6: 9. 15 (1H, s), 8. 60 (1H, d, J=1. 9Hz), 8. 43 (2H, d, J=5. 8Hz), 8. 32 (1H, d, J=2. 4Hz), 8. 07 (1H, d, J=8. 6Hz), 7. 84 (1H, dd, J=8. 6, 1. 9Hz), 7. 52 (1H, d, J=2. 4Hz), 7. 36 (2H, d, J=5. 8Hz), 4. 88 (2H, s), 3. 90 (2H, s), 1. 44 (9H, s)	149. 6-150. 8
90	3000, 1601, 1504, 1473, 1433, 1336, 1228	DMSO-d6: 9. 01 (1H, s), 8. 50 (1H, d, J=2. 0 Hz), 8. 19 (1H, d, J=2. 2Hz), 8. 01 (1H, d, J=8. 8Hz), 7. 77 (1H, dd, J=8. 8, 2. 0Hz), 7. 54 (1H, d, J=2. 2Hz), 7. 39～7. 37 (2H, m), 7. 30～7. 23 (2H, m), 7. 18～7. 13 (1H, m), 3. 93 (3H, s), 3. 88 (2H, s)	324. 6 (decomposition)
91	3323, 1574, 1448, 1421, 1390, 1325	DMSO-d6: 10. 14 (1H, bs), 9. 04 (1H, s), 8. 53 (1H, d, J=1. 6Hz), 8. 05 (1H, d, J=8. 6Hz), 8. 01 (1H, d, J=2. 4Hz), 7. 78 (1H, dd, J=8. 6, 1. 6Hz), 7. 50 (1H, d, J=2. 4Hz), 7. 37 (2H, d, J=7. 3Hz), 7. 26 (2H, dd, J=7. 3, 5. 9Hz), 7. 17 (1H, d, J=5. 9Hz), 3. 87 (2H, s)	315. 2 (decomposition)
92	3000, 1603, 1504, 1473, 1336, 1248, 1228	DMSO-d6: 9. 02 (1H, s), 8. 57 (1H, d, J=2. 0 Hz), 8. 26 (1H, d, J=2. 4Hz), 8. 07 (1H, d, J=8. 8Hz), 7. 80 (1H, dd, J=8. 8, 2. 0Hz), 7. 58 (1H, d, J=2. 4Hz), 7. 29 (2H, d, J=8. 8Hz), 6. 82 (2H, d, J=8. 8Hz), 3. 95 (3H, s), 3. 82 (2H, s), 3. 69 (3H, s)	190. 2-194. 2
93	3305, 1578, 1564, 1510, 1448, 1327, 1234	*DMSO-d6: 10. 12 (1H, s), 9. 13 (1H, s), 8. 96 (1H, s), 8. 54 (1H, d, J=1. 8Hz), 8. 07～8. 01 (2H, m), 7. 78 (1H, dd, J=9. 0, 1. 8Hz), 7. 50 (1H, d, J=2. 2Hz), 7. 16～7. 14 (2H, m), 6. 66～6. 63 (2H, m), 3. 75 (2H, s)	300. 0 (decomposition)
94	3100, 1649, 1601, 1504, 1333, 735	DMSO-d6: 9. 02 (1H, s), 8. 58 (1H, d, J=2. 0 Hz), 8. 28 (1H, d, J=2. 0Hz), 8. 09 (1H, d, J=8. 5Hz), 7. 80 (1H, dd, J=8. 5, 2. 0Hz), 7. 60 (1H, d, J=2. 0Hz), 7. 52～7. 49 (1H, m), 6. 34 (1H, dd, J=2. 7, 2. 4Hz), 6. 12 (1H, d, J=2. 7Hz), 3. 96 (3H, s), 3. 92 (2H, s)	154. 9-159. 4
95	3000, 1597, 1508, 1338, 1273, 1020	DMSO-d6: 9. 30 (1H, s), 8. 60～8. 59 (2H, m), 8. 29 (1H, d, J=2. 2Hz), 8. 11 (1H, d, J=8. 8Hz), 7. 93 (1H, d, J=1. 0Hz), 7. 86～7. 83 (1H, m), 7. 58 (1H, d, J=2. 2Hz), 5. 32 (2H, s), 3. 95 (3H, s)	272. 1 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
96	3300, 1581, 1506, 1450, 1421, 1327, 1273	DMSO-d6: 10. 24 (1H, s), 9. 26 (1H, s), 8. 60~8. 56 (2H, m), 8. 09 (1H, d, J=8. 8Hz), 8. 04 (1H, m), 7. 93 (1H, s), 7. 83~7. 80 (1H, m), 7. 49 (1H, d, J=1. 0Hz), 5. 30 (2H, s)	300. 0 (decomposition)
97	3000, 1768, 1605, 1506, 1329, 1198, 1147	DMSO-d6: 9. 37 (1H, s), 8. 62~8. 58 (2H, m), 8. 47~8. 43 (1H, m), 8. 15 (1H, d, J=8. 3Hz), 7. 94~7. 79 (3H, m), 5. 32 (2H, s), 2. 38 (3H, s)	244. 3 (decomposition)
98	1728, 1680, 1657, 1554, 1502, 1230, 1155	*DMSO-d6: 9. 47 (1H, s), 8. 55 (1H, d, J=1. 9Hz), 8. 30 (1H, d, J=8. 7Hz), 8. 23 (1H, d, J=2. 2Hz), 7. 81 (1H, dd, J=8. 7, 1. 9Hz), 7. 56 (1H, d, J=2. 2Hz), 4. 31 (2H, q, J=7. 1Hz), 3. 90 (3H, s), 1. 35 (3H, t, J=7. 1Hz)	240. 4-249. 4
99	1718, 1547, 1473, 806	*DMSO-d6: 14. 79 (1H, s), 9. 93 (1H, s), 8. 63 (1H, d, J=1. 9Hz), 8. 52 (1H, d, J=8. 5Hz), 8. 42 (1H, d, J=2. 3Hz), 7. 88 (1H, dd, J=8. 5, 1. 9Hz), 7. 72 (1H, d, J=2. 3Hz), 4. 01 (3H, s)	333. 7 (decomposition)
100	1606, 1473, 1319, 1238, 802	*DMSO-d6: 9. 24 (1H, s), 8. 60 (1H, d, J=2. 0Hz), 8. 31 (1H, d, J=2. 2Hz), 8. 20 (1H, d, J=8. 7Hz), 7. 82 (1H, dd, J=8. 7, 2. 0Hz), 7. 62 (1H, d, J=2. 2Hz), 3. 98 (3H, s), 3. 69~3. 64 (4H, m), 3. 62~3. 53 (2H, m), 3. 40~3. 31 (2H, m)	317. 4 (decomposition)
101	1603, 1508, 1468, 1425, 1385, 802	*DMSO-d6: 9. 18 (1H, s), 8. 67~8. 62 (1H, m), 8. 48~8. 44 (1H, m), 8. 39 (1H, d, J=4. 9Hz), 8. 25~8. 23 (2H, m), 7. 77 (1H, d, J=7. 9Hz), 7. 65 (1H, d, J=8. 1Hz), 7. 58 (1H, d, J=2. 4Hz), 7. 28 (1H, dd, J=7. 9, 4. 9Hz), 3. 95 (3H, s), 3. 89 (2H, s)	280. 5-285. 3
102	3307, 1576, 1572, 1512, 1448, 1392, 901	*DMSO-d6: 10. 13 (1H, s), 9. 11 (1H, s), 8. 61 (1H, s), 8. 41 (1H, d, J=1. 7Hz), 8. 37~8. 35 (1H, m), 8. 18 (1H, d, J=8. 3Hz), 7. 96 (1H, d, J=2. 2Hz), 7. 78~7. 72 (1H, m), 7. 64~7. 56 (1H, m), 7. 47 (1H, d, J=2. 2Hz), 7. 27 (1H, dd, J=7. 9, 4. 6Hz), 3. 85 (2H, s)	355. 0 (decomposition)
103	3000, 1753, 1605, 1508, 1383, 1236, 1149	*DMSO-d6: 9. 15 (1H, s), 8. 63 (1H, s), 8. 43 (1H, d, J=1. 4Hz), 8. 39~8. 38 (1H, m), 8. 25 (1H, d, J=2. 2Hz), 8. 21 (1H, d, J=8. 3Hz), 7. 76 (1H, d, J=7. 8Hz), 7. 63 (1H, dd, J=8. 3, 1. 4Hz), 7. 51 (1H, d, J=2. 2Hz), 7. 28 (1H, dd, J=7. 8, 4. 7Hz), 4. 87 (2H, s), 3. 88 (2H, s), 1. 44 (9H, s)	230. 1-232. 0

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
104	1603, 1578, 1508, 1468, 1389, 1059	*DMSO-d6: 9. 17 (1H, s), 8. 65～8. 61 (1H, m), 8. 45 (1H, d, J=1. 6Hz), 8. 42～8. 35 (1H, m), 8. 28 (1H, d, J=2. 3Hz), 8. 24 (1H, d, J=8. 4Hz), 7. 80～7. 73 (1H, m), 7. 64 (1H, dd, J=8. 4, 1. 6Hz), 7. 52 (1H, d, J=2. 3Hz), 7. 28 (1H, dd, J=7. 7, 4. 7Hz), 4. 91 (2H, s), 3. 88 (2H, s)	188. 9-191. 9
105	1589, 1578, 1506, 1389, 1030, 814, 716	*DMSO-d6: 9. 15 (1H, s), 8. 75 (1H, s), 8. 64 (1H, s), 8. 58～8. 56 (1H, m), 8. 46～8. 43 (1H, m), 8. 39～8. 38 (1H, m), 8. 34～8. 31 (1H, m), 8. 20 (1H, d, J=8. 4Hz), 7. 95 (1H, d, J=7. 7Hz), 7. 77 (1H, d, J=7. 6Hz), 7. 69～7. 67 (1H, m), 7. 65～7. 62 (1H, m), 7. 46 (1H, dd, J=7. 7, 4. 9Hz), 7. 29 (1H, dd, J=7. 6, 5. 2Hz), 5. 36 (2H, s), 3. 99 (2H, s)	218. 8-223. 2
106	1738, 1605, 1506, 1473, 1232, 1055	*DMSO-d6: 9. 18 (1H, s), 8. 72 (1H, s), 8. 66～8. 62 (1H, m), 8. 61～8. 56 (1H, m), 8. 48～8. 46 (1H, m), 8. 39 (1H, d, J=4. 8Hz), 8. 37～8. 35 (1H, m), 8. 23 (1H, d, J=8. 5Hz), 7. 96 (1H, s), 7. 78～7. 76 (1H, m), 7. 73～7. 68 (1H, m), 7. 66 (1H, d, J=8. 5Hz), 7. 29 (1H, dd, J=7. 7, 4. 8Hz), 5. 39 (2H, s), 5. 16 (2H, s), 3. 89 (2H, s), 2. 07 (3H, s)	202. 7-205. 9
107	3167, 1599, 1506, 1471, 1387, 1028, 712	*DMSO-d6: 9. 17 (1H, s), 8. 67～8. 61 (2H, m), 8. 53～8. 50 (1H, m), 8. 41 (1H, d, J=1. 6Hz), 8. 39 (1H, d, J=4. 8Hz), 8. 34 (1H, d, J=2. 2Hz), 8. 21 (1H, d, J=8. 3Hz), 7. 93～7. 87 (1H, m), 7. 77 (1H, d, J=7. 8Hz), 7. 69 (1H, d, J=2. 2Hz), 7. 65 (1H, dd, J=8. 3, 1. 6Hz), 7. 29 (1H, dd, J=7. 8, 4. 8Hz), 5. 45～5. 24 (3H, m), 4. 47 (2H, s), 3. 88 (2H, s)	143. 1-146. 8
108	1645, 1601, 1578, 1506, 1468, 1389	*DMSO-d6: 9. 20 (1H, s), 9. 17 (1H, s), 9. 00 (2H, s), 8. 64 (1H, d, J=1. 7Hz), 8. 46 (1H, d, J=1. 5Hz), 8. 39 (1H, dd, J=4. 5, 1. 7Hz), 8. 36 (1H, d, J=2. 2Hz), 8. 22 (1H, d, J=8. 1Hz), 7. 77 (1H, dt, J=7. 8, 1. 7Hz), 7. 72 (1H, d, J=2. 2Hz), 7. 65 (1H, dd, J=8. 1, 1. 5Hz), 7. 29 (1H, dd, J=7. 8, 4. 5Hz), 5. 40 (2H, s), 3. 89 (2H, s)	229. 2-233. 5

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
109	3055, 1659, 1601, 1579, 1506, 1389, 1059	*DMSO-d6:9. 16(1H, s), 8. 63(1H, d, J=1. 6Hz), 8. 44(1H, d, J=1. 5Hz), 8. 39(1H, dd, J=4. 7, 1. 6Hz), 8. 34~8. 23(2H, m), 8. 20(1H, d, J=8. 4Hz), 7. 78~7. 75(1H, m), 7. 67~7. 58(2H, m), 7. 29(1H, dd, J=8. 0, 4. 7Hz), 4. 67(2H, s), 3. 94(2H, s), 3. 23~3. 14(2H, m), 1. 06(3H, t, J=7. 2Hz)	263. 0-266. 2
110	1597, 1578, 1506, 1462, 1389, 1057	*DMSO-d6:9. 13(1H, s), 8. 64(1H, s), 8. 43~8. 36(2H, m), 8. 20(1H, d, J=2. 2Hz), 8. 19(1H, d, J=8. 3Hz), 7. 77(1H, d, J=7. 8Hz), 7. 62(1H, dd, J=8. 3, 1. 7Hz), 7. 54(1H, d, J=2. 2Hz), 7. 29(1H, dd, J=7. 8, 4. 7Hz), 4. 62(1H, t, J=5. 2Hz), 4. 21(2H, t, J=6. 4Hz), 3. 87(2H, s), 3. 65~3. 59(2H, m), 2. 00~1. 90(2H, m)	221. 6-222. 8
111	1711, 1601, 1504, 1385, 719	*DMSO-d6:9. 16(1H, s), 8. 63(1H, s), 8. 45(1H, s), 8. 38(1H, d, J=4. 6Hz), 8. 16(1H, d, J=8. 1Hz), 8. 06(1H, s), 7. 87~7. 72(5H, m), 7. 67~7. 61(1H, m), 7. 47(1H, s), 7. 35~7. 31(1H, m), 4. 26~4. 16(2H, m), 3. 87(2H, s), 3. 83(2H, t, J=6. 8Hz), 2. 19~2. 08(2H, m)	231. 9-136. 7
112	3444, 3431, 1643, 1601, 1576, 1506, 1462	*DMSO-d6:9. 24(1H, s), 8. 64(1H, s), 8. 49(1H, d, J=1. 6Hz), 8. 38(1H, d, J=4. 7Hz), 8. 33~8. 27(1H, m), 8. 25(1H, d, J=8. 4Hz), 7. 78(1H, d, J=7. 9Hz), 7. 65(1H, dd, J=8. 4, 1. 6Hz), 7. 61(1H, d, J=2. 4Hz), 7. 29(1H, dd, J=7. 9, 4. 7Hz), 4. 21(2H, t, J=6. 5Hz), 3. 87(2H, s), 3. 04~2. 93(2H, m), 2. 19~2. 07(2H, m)	253. 2 (decomposition)
113	1593, 1579, 1508, 1473, 1300, 1036	*DMSO-d6:8. 95(1H, s), 8. 41(1H, d, J=1. 5Hz), 8. 20(1H, d, J=8. 3Hz), 8. 19(1H, d, J=2. 3Hz), 7. 61(1H, dd, J=8. 3, 1. 5Hz), 7. 57(1H, d, J=2. 3Hz), 3. 96(3H, s), 2. 10(3H, s)	238. 4 (decomposition)
114	1597, 1579, 1450, 1429, 1302, 1209, 1055	*DMSO-d6:8. 95(1H, s), 8. 42(1H, d, J=1. 5Hz), 8. 19(1H, d, J=8. 3Hz), 7. 97(1H, d, J=2. 0Hz), 7. 59(1H, dd, J=8. 3, 1. 5Hz), 7. 51(1H, d, J=2. 0Hz), 2. 09(3H, s)	300. 0 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
115	1603, 1579, 1504, 1427, 1302	*DMSO-d6:8. 98 (1H, s), 8. 77 (1H, bs), 8. 58 (1H, dd, J=4. 9, 1. 5Hz), 8. 44 (1H, d, J=1. 3Hz), 8. 33 (1H, d, J=2. 1Hz), 8. 21 (1H, d, J=8. 3Hz), 7. 98~7. 95 (1H, m), 7. 72 (1H, d, J=2. 1Hz), 7. 63 (1H, dd, J=8. 3, 1. 3Hz), 7. 47 (1H, dd, J=7. 6, 4. 9Hz), 5. 38 (2H, s), 2. 11 (3H, s)	203. 1 (decomposition)
116	1597, 1506, 1468, 1383, 1290, 1028, 818	*DMSO-d6:8. 94 (1H, d, J=7. 6Hz), 8. 49 (1H, d, J=1. 6Hz), 8. 25~8. 22 (2H, m), 7. 65 (1H, dd, J=8. 4, 1. 6Hz), 7. 57 (1H, d, J=2. 4Hz), 6. 38 (1H, d, J=7. 6Hz), 3. 97 (3H, s)	279. 0 (decomposition)
117	3000, 1606, 1508, 1450, 1398, 1188, 818	*DMSO-d6:8. 87 (1H, d, J=7. 6Hz), 8. 44 (1H, d, J=1. 5Hz), 8. 14 (1H, d, J=8. 3Hz), 7. 93 (1H, d, J=1. 9Hz), 7. 58 (1H, dd, J=8. 3, 1. 5Hz), 7. 45 (1H, d, J=1. 9Hz), 6. 29 (1H, d, J=7. 6Hz)	350. 0<
118	1755, 1601, 1506, 1246, 1153, 814	*DMSO-d6:8. 93 (1H, d, J=7. 7Hz), 8. 48 (1H, d, J=1. 7Hz), 8. 26 (1H, d, J=2. 4Hz), 8. 22 (1H, d, J=8. 3Hz), 7. 64 (1H, dd, J=8. 3, 1. 7Hz), 7. 51 (1H, d, J=2. 4Hz), 6. 36 (1H, d, J=7. 7Hz), 4. 90 (2H, s), 1. 44 (9H, s)	230. 3-231. 5
119	1647, 1606, 1578, 1504, 1464, 1196, 822	*DMSO-d6:13. 15 (1H, bs), 8. 93 (1H, d, J=7. 7Hz), 8. 48 (1H, d, J=1. 6Hz), 8. 26 (1H, d, J=2. 3Hz), 8. 22 (1H, d, J=8. 4Hz), 7. 64 (1H, dd, J=8. 4, 1. 6Hz), 7. 51 (1H, d, J=2. 3Hz), 6. 37 (1H, d, J=7. 7Hz), 4. 93 (2H, s)	350. 0 (decomposition)
120	1605, 1504, 1288, 1194, 1059, 820	*DMSO-d6:8. 95 (1H, d, J=7. 6Hz), 8. 76 (1H, d, J=1. 7Hz), 8. 58 (1H, dd, J=4. 9, 1. 7Hz), 8. 50 (1H, d, J=1. 6Hz), 8. 36 (1H, d, J=2. 3Hz), 8. 22 (1H, d, J=8. 2Hz), 7. 99~7. 94 (1H, m), 7. 70 (1H, d, J=2. 3Hz), 7. 66 (1H, dd, J=8. 2, 1. 6Hz), 7. 49~7. 44 (1H, m), 6. 38 (1H, d, J=7. 6Hz), 5. 39 (2H, s)	262. 0 (decomposition)
121	1599, 1581, 1506, 1473, 1425, 1230	*DMSO-d6:9. 12 (1H, s), 8. 46 (1H, d, J=1. 5Hz), 8. 24~8. 19 (2H, m), 7. 63 (1H, dd, J=8. 4, 1. 5Hz), 7. 57 (1H, d, J=2. 2Hz), 7. 41~7. 35 (2H, m), 7. 29~7. 23 (2H, m), 7. 19~7. 13 (1H, m), 3. 95 (3H, s), 3. 88 (2H, s)	254. 0-258. 6
122	1603, 1579, 1512, 1439, 1390, 1308	*DMSO-d6:10. 10 (1H, s), 9. 10 (1H, s), 8. 46 (1H, d, J=1. 6Hz), 8. 20 (1H, d, J=8. 2Hz), 7. 98 (1H, d, J=2. 2Hz), 7. 60 (1H, dd, J=8. 2, 1. 6Hz), 7. 49 (1H, d, J=2. 2Hz), 7. 40~7. 35 (2H, m), 7. 29~7. 23 (2H, m), 7. 19~7. 12 (1H, m), 3. 88 (2H, s)	350. 0 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
123	3435, 1605, 1581, 1508, 1470, 1429, 1385	*DMSO-d6: 9. 14 (1H, s), 8. 45~8. 42 (2H, m), 8. 24~8. 21 (3H, m), 7. 66~7. 60 (1H, m), 7. 58~7. 56 (2H, m), 3. 94 (3H, s), 3. 83 (2H, s), 2. 22 (3H, s)	285. 3-286. 4
124	1601, 1576, 1504, 1454, 1389, 1271	*DMSO-d6: 9. 09 (1H, s), 8. 46~8. 38 (2H, m), 8. 21 (1H, d, J=1. 9Hz), 8. 16 (1H, d, J=8. 2Hz), 7. 96~7. 89 (1H, m), 7. 63~7. 54 (2H, m), 7. 42~7. 45 (1H, m), 3. 82 (2H, s), 2. 23 (3H, s)	300. 0 (decomposition)
125	1605, 1581, 1508, 1470, 1404, 1385	*DMSO-d6: 9. 16 (1H, s), 9. 02 (1H, s), 8. 83 (2H, s), 8. 42 (1H, d, J=1. 6Hz), 8. 24~8. 22 (2H, m), 7. 64 (1H, dd, J=8. 3, 1. 6Hz), 7. 57 (1H, d, J=2. 4), 3. 95 (3H, s), 3. 88 (2H, s)	266. 6-272. 0
126	3304, 1603, 1572, 1514, 1450, 1437, 1394	*DMSO-d6: 9. 11 (1H, s), 9. 01 (1H, s), 8. 82 (2H, s), 8. 39 (1H, d, J=1. 7Hz), 8. 17 (1H, d, J=8. 4Hz), 7. 94 (1H, d, J=1. 9), 7. 60 (1H, dd, J=8. 4, 1. 7Hz), 7. 44 (1H, d, J=1. 9), 3. 86 (2H, s)	375. 0 (decomposition)
127	3024, 1610, 1510, 1452, 1340, 760	DMSO-d6: 9. 17 (1H, s), 8. 53 (1H, d, J=7. 6Hz), 8. 46~8. 44 (1H, m), 8. 31 (1H, d, J=7. 8Hz), 8. 18 (1H, d, J=7. 8Hz), 8. 11 (1H, d, J=7. 8Hz), 7. 74~7. 63 (3H, m), 7. 49 (1H, t, J=7. 8Hz), 7. 39 (1H, d, J=7. 6Hz), 7. 21~7. 17 (1H, m), 4. 07 (2H, s)	167. 4-168. 1
128	1643, 1608, 1454, 1333, 754	DMSO-d6: 9. 22 (1H, s), 8. 68~8. 63 (1H, m), 8. 52 (1H, d, J=8. 0Hz), 8. 38 (1H, d, J=4. 8Hz), 8. 29 (1H, d, J=7. 7Hz), 8. 15~8. 10 (2H, m), 7. 78 (1H, d, J=7. 8Hz), 7. 70 (1H, t, J=8. 0Hz), 7. 66 (1H, t, J=7. 7Hz), 7. 48 (1H, t, J=7. 7Hz), 7. 28 (1H, dd, J=7. 8, 4. 8Hz), 3. 92 (2H, s)	223. 5-224. 1
129	3022, 1643, 1599, 1454, 756	DMSO-d6: 9. 23 (1H, s), 8. 53 (1H, d, J=7. 8Hz), 8. 45 (2H, d, J=5. 6Hz), 8. 30 (1H, d, J=7. 8Hz), 8. 13 (1H, d, J=7. 8Hz), 8. 12 (1H, d, J=7. 8Hz), 7. 74~7. 64 (2H, m), 7. 49 (1H, t, J=7. 8Hz), 7. 38 (2H, d, J=5. 6Hz), 3. 93 (2H, s)	193. 1-194. 8

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
130	3010, 1600, 1452, 1335, 762	DMSO-d6: 9. 18 (1H, s), 8. 52 (1H, d, J=7. 7 Hz), 8. 30 (1H, d, J=7. 8Hz), 8. 13 (1H, d, J=7. 8Hz), 8. 12 (1H, d, J=7. 7Hz), 7. 70 (1H, t, J=7. 7Hz), 7. 66 (1H, t, J=7. 8Hz), 7. 48 (1H, t, J=7. 8Hz), 7. 42 (2H, d, 8. 6Hz), 7. 31 (2H, d, J=8. 6Hz), 3. 90 (2H, s)	187. 9-188. 5
131	3000, 1602, 1454, 1336, 760	DMSO-d6: 9. 10 (1H, s), 8. 51 (1H, d, J=7. 7 Hz), 8. 29 (1H, d, J=7. 8Hz), 8. 13 (1H, d, J=7. 8Hz), 8. 12 (1H, d, J=7. 7Hz), 7. 70 (1H, t, J=7. 7Hz), 7. 65 (1H, t, J=7. 8Hz), 7. 47 (1H, t, J=7. 8Hz), 7. 31 (2H, d, 8. 6Hz), 6. 83 (2H, d, J=8. 6Hz), 3. 84 (2H, s), 3. 69 (3H, s)	148. 6-149. 2
132	3192, 1641, 1579, 1562, 1452, 760	DMSO-d6: 9. 13 (1H, s), 9. 06 (1H, s), 8. 50 (1H, d, J=7. 5Hz), 8. 28 (1H, d, J=7. 4Hz), 8. 18～8. 11 (2H, m), 7. 69 (1H, t, J=7. 5Hz), 7. 64 (1H, t, J=7. 4Hz), 7. 47 (1H, t, J=7. 4Hz), 7. 18 (2H, d, J=8. 1Hz), 6. 66 (2H, d, J=8. 1Hz), 3. 80 (2H, s)	268. 2-270. 3
133	3053, 1707, 1610, 1508, 1277, 760	DMSO-d6: 9. 21 (1H, s), 8. 53 (1H, d, J=7. 4 Hz), 8. 31 (1H, d, J=7. 7Hz), 8. 14 (1H, d, J=7. 7Hz), 8. 12 (1H, d, J=7. 4Hz), 7. 87 (2H, d, J=7. 9Hz), 7. 71 (1H, t, J=7. 4Hz), 7. 67 (1H, t, J=7. 7Hz), 7. 55～7. 46 (3H, m), 4. 28 (2H, q, J=7. 0Hz), 4. 04 (2H, s), 1. 29 (3H, t, J=7. 0Hz)	161. 7-162. 3
134	3051, 1709, 1643, 1610, 1510, 1335, 758	DMSO-d6: 12. 79 (1H, bs), 9. 23 (1H, s), 8. 54 (1H, d, J=7. 7Hz), 8. 31 (1H, d, J=7. 5Hz), 8. 15 (1H, d, J=7. 5Hz), 8. 12 (1H, d, J=7. 7 Hz), 7. 85 (2H, d, J=8. 2Hz), 7. 72 (1H, t, J=7. 7Hz), 7. 67 (1H, t, J=7. 5Hz), 7. 52～7. 47 (3H, m), 3. 99 (2H, s)	248. 8-252. 9
135	3427, 1641, 1606, 1568, 1454, 756	DMSO-d6: 9. 02 (1H, s), 8. 52 (1H, d, J=7. 5 Hz), 8. 29 (1H, d, J=7. 7Hz), 8. 14～8. 11 (2H, m), 7. 70 (1H, t, J=7. 5Hz), 7. 65 (1H, t, J=7. 7Hz), 7. 47 (1H, t, J=7. 7Hz), 7. 04 (2H, d, J=8. 2Hz), 6. 47 (2H, d, J=8. 2Hz), 4. 84 (2H, bs), 3. 73 (2H, s)	228. 3-232. 6
136	3047, 1641, 1606, 1454, 1333, 762	DMSO-d6: 9. 19 (1H, s), 8. 54 (1H, d, J=7. 9 Hz), 8. 31 (1H, d, J=7. 7Hz), 8. 16 (1H, d, J=7. 7Hz), 8. 14 (1H, d, J=7. 9Hz), 7. 76～7. 63 (2H, m), 7. 49 (1H, t, J=7. 7Hz), 7. 28 (1H, dd, J=5. 3, 1. 3Hz), 7. 02～6. 88 (2H, m), 4. 11 (2H, s)	174. 3-175. 2

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
137	3232, 1587, 1512, 1335, 1228, 798, 741	DMSO-d6: 10. 49 (1H, bs), 8. 93 (1H, s), 8. 52 (1H, d, J=7. 6Hz), 8. 30 (1H, d, J=7. 6Hz), 8. 15 (1H, d, J=7. 9Hz), 8. 06 (1H, d, J=7. 9 Hz), 7. 74~7. 62 (2H, m), 7. 48 (1H, t, J=7. 6Hz), 6. 60~6. 58 (1H, m), 5. 90~5. 88 (1H, m), 5. 82 (1H, s), 3. 87 (2H, s)	255. 1-258. 1
138	3273, 1570, 1512, 1335, 1086, 760	DMSO-d6: 11. 63 (1H, bs), 9. 11 (1H, s), 8. 54 (1H, d, J=7. 3Hz), 8. 31 (1H, d, J=7. 6Hz), 8. 16~8. 10 (2H, m), 7. 75~7. 69 (1H, m), 7. 69~7. 63 (1H, m), 7. 49 (1H, t, J=7. 6Hz), 6. 95 (1H, s), 6. 76 (1H, s), 3. 96 (2H, s)	290. 9-292. 8
139	1610, 1506, 1452, 1333, 762	DMSO-d6: 8. 93 (1H, s), 8. 50 (1H, d, J=6. 9 Hz), 8. 34~8. 25 (2H, m), 8. 19~8. 16 (1H, m), 8. 02 (1H, d, J=8. 3Hz), 7. 94~7. 91 (1H, m), 7. 85~7. 76 (1H, m), 7. 71 (1H, t, J=7. 6Hz), 7. 61~7. 38 (6H, m), 4. 39 (2H, s)	196. 4-197. 2
140	3045, 1643, 1610, 1502, 1452, 1335, 760	DMSO-d6: 9. 24 (1H, s), 8. 53 (1H, d, J=7. 6 Hz), 8. 31 (1H, d, J=7. 9Hz), 8. 18~8. 11 (2H, m), 7. 84~7. 81 (4H, m), 7. 74~7. 57 (3H, m), 7. 52~7. 40 (3H, m), 4. 10 (2H, s)	165. 7-167. 1
141	1610, 1510, 1454, 1336, 756	DMSO-d6: 9. 31 (1H, s), 9. 02 (1H, d, J=1. 7 Hz), 8. 59~8. 57 (1H, m), 8. 31 (1H, d, J=7. 6Hz), 8. 25 (1H, d, J=1. 7Hz), 8. 19~8. 07 (2H, m), 7. 97 (1H, d, J=8. 3Hz), 7. 92~7. 86 (1H, m), 7. 74~7. 65 (3H, m), 7. 57~7. 47 (2H, m), 4. 12 (2H, s)	231. 5-232. 4
142	3379, 1608, 1510, 1452, 1109, 758, 744	DMSO-d6: 10. 81 (1H, s), 9. 00 (1H, s), 8. 49 (1H, d, J=7. 3Hz), 8. 26 (1H, d, J=7. 9Hz), 8. 15 (1H, d, J=7. 9Hz), 8. 07 (1H, d, J=8. 3Hz), 7. 72~7. 69 (2H, m), 7. 68~7. 57 (1H, m), 7. 47~7. 36 (1H, m), 7. 32 (1H, d, J=7. 9Hz), 7. 20 (1H, s), 7. 06~6. 93 (2H, m), 4. 02 (2H, s)	153. 6-155. 6
143	3055, 2924, 1738, 1643, 1610, 1506, 1454, 760	CDCl3: 8. 33 (1H, d, J=7. 9Hz), 8. 23 (1H, d, J=7. 6Hz), 8. 15 (1H, s), 8. 08 (1H, d, J=7. 6 Hz), 7. 71~7. 53 (3H, m), 7. 41 (1H, t, J=7. 6Hz), 2. 57~2. 54 (2H, m), 1. 83~1. 68 (6H, m), 1. 32~1. 02 (5H, m)	oil

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
144	3059, 2997, 1608, 1508, 754	DMSO-d6: 8. 97 (1H, s), 8. 52 (1H, d, J=7. 3 Hz), 8. 30 (1H, d, J=7. 6Hz), 8. 18 (1H, d, J=7. 3Hz), 8. 16 (1H, d, J=7. 6Hz), 7. 71 (1H, t, J=7. 6Hz), 7. 66 (1H, t, J=7. 3Hz), 7. 48 (1H, t, J=7. 6Hz), 2. 53～2. 40 (2H, m), 1. 24～1. 09 (1H, m), 0. 53～0. 47 (2H, m), 0. 29～0. 24 (2H, m)	148. 3-151. 0
145	1643, 1616, 1452, 762	DMSO-d6: 9. 43 (1H, s), 8. 59 (1H, d, J=6. 8 Hz), 8. 34 (1H, d, J=7. 5Hz), 8. 32 (1H, d, J=7. 5Hz), 8. 14 (1H, d, J=6. 8Hz), 7. 91～7. 88 (2H, m), 7. 79 (1H, t, J=7. 5Hz), 7. 70～7. 63 (2H, m), 7. 57～7. 49 (3H, m)	287. 0-289. 0
146	3363, 1641, 1564, 1452, 1223, 1171, 760	DMSO-d6: 9. 13 (1H, s), 8. 54 (1H, d, J=7. 6 Hz), 8. 33 (1H, d, J=7. 6Hz), 8. 31 (1H, d, J=7. 6Hz), 8. 10 (1H, d, J=7. 6Hz), 7. 71 (1H, t, J=7. 6Hz), 7. 66 (1H, t, J=7. 6Hz), 7. 58～7. 46 (3H, m), 7. 30～7. 15 (3H, m), 5. 99～5. 93 (2H, m)	202. 0-206. 3
147	3294, 1601, 1500, 1437, 1317, 758	DMSO-d6: 9. 06 (1H, s), 8. 59 (1H, d, J=7. 9 Hz), 8. 33 (1H, d, J=7. 5Hz), 8. 29～8. 25 (2H, m), 7. 74 (1H, t, J=7. 9Hz), 7. 64 (1H, t, J=7. 5Hz), 7. 48 (1H, t, J=7. 5Hz), 7. 31～7. 26 (4H, m), 6. 87～6. 82 (1H, m)	207. 8-210. 3
148	3047, 1639, 1603, 1502, 1479, 1452, 1350, 750	DMSO-d6: 9. 31 (1H, s), 8. 58 (1H, d, J=7. 3 Hz), 8. 33 (1H, d, J=7. 9Hz), 8. 23 (1H, d, J=7. 9Hz), 8. 16 (1H, d, J=7. 6Hz), 7. 74 (1H, t, J=7. 6Hz), 7. 69～7. 61 (1H, m), 7. 54～7. 47 (1H, m), 7. 14 (2H, t, J=7. 3Hz), 6. 83～6. 62 (3H, m), 3. 28 (3H, s)	166. 3-170. 8
149	3051, 1608, 1321, 1304, 1238, 766, 746	DMSO-d6: 9. 44 (1H, s), 8. 61 (1H, d, J=7. 3 Hz), 8. 35 (1H, d, J=7. 9Hz), 8. 22～8. 18 (2H, m), 7. 79～7. 73 (1H, m), 7. 66 (1H, dd, J=7. 9, 7. 6Hz), 7. 51 (1H, dd, J=7. 6, 7. 3Hz), 7. 33～7. 28 (2H, m), 7. 28～6. 99 (3H, m)	210. 0-211. 3
150	3051, 1618, 1506, 1450, 1227, 716	DMSO-d6: 9. 71 (1H, s), 8. 58 (1H, d, J=7. 6 Hz), 8. 33～8. 26 (2H, m), 8. 20 (1H, d, J=7. 9Hz), 7. 78 (1H, dd, J=7. 9, 7. 6Hz), 7. 67 (1H, dd, J=7. 9, 7. 6Hz), 7. 52 (1H, dd, J=7. 6, 7. 2Hz)	248. 2-250. 1

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
151	1643, 1610, 1566, 1510, 1454, 1227, 762	DMSO-d6:8. 89(1H, s), 8. 54(1H, d, J=7. 3 Hz), 8. 31(1H, d, J=7. 6Hz), 8. 27(1H, d, J= 8. 3Hz), 8. 16(1H, d, J=7. 9Hz), 7. 76~7. 70(1H, m), 7. 64(1H, t, J=7. 3Hz), 7. 52~7. 46(1H, m), 4. 93~4. 81(1H, m), 1. 94~1. 53(2H, m), 0. 95(3H, t, J=7. 3Hz)	87. 3 (decomposition)
152	1612, 1572, 1510, 1309, 756	DMSO-d6:9. 03(1H, s), 8. 53(1H, d, J=7. 8 Hz), 8. 30(1H, d, J=7. 8Hz), 8. 18~8. 10(2H, m), 7. 74~7. 63(2H, m), 7. 48(1H, dd, J= 7. 8, 7. 3Hz), 2. 15(3H, s)	300. 0 (decomposition)
153	1608, 1504, 1306, 1134, 762	DMSO-d6:9. 40(1H, s), 8. 62(1H, s), 8. 56 (1H, d, J=7. 3Hz), 8. 32(1H, d, J=7. 8Hz), 8. 20~8. 12(2H, m), 7. 94(1H, s), 7. 77~7. 66(2H, m), 7. 52(1H, dd, J=7. 8, 7. 3Hz), 5. 34(2H, s)	228. 8 (decomposition)
154	1593, 1508, 1464, 1228, 752	DMSO-d6:9. 14(1H, s), 8. 64(1H, d, J=1. 6 Hz), 8. 38(1H, dd, J=4. 8, 1. 6Hz), 8. 26(1H, d, J=7. 6Hz), 8. 18(1H, d, J=2. 2Hz), 8. 09 (1H, d, J=7. 6Hz), 7. 77(1H, d, J=7. 8Hz), 7. 65(1H, t, J=7. 6Hz), 7. 54(1H, d, J=2. 2Hz), 7. 46(1H, t, J=7. 6Hz), 7. 28(1H, dd, J=7. 8, 4. 8Hz), 3. 95(3H, s), 3. 91(2H, s)	192. 9-193. 7
155	3533, 3398, 1568, 1516, 1394, 1319, 1296	DMSO-d6:10. 07(1H, s), 9. 12(1H, s), 8. 64(1H, s), 8. 38(1H, bs), 8. 24(1H, d, J=7. 3 Hz), 8. 08(1H, d, J=8. 3Hz), 7. 96(1H, d, J= 2. 0Hz), 7. 77(1H, d, J=7. 8Hz), 7. 64(1H, dd, J=8. 3, 7. 3Hz), 7. 47~7. 41(2H, m), 7. 30~7. 26(1H, m), 3. 89(2H, s)	306. 5 (decomposition)
156	1755, 1599, 1572, 1508, 1458, 1190	DMSO-d6:9. 14(1H, s), 8. 65(1H, s), 8. 40 ~8. 38(2H, m), 8. 29(1H, d, J=7: 8Hz), 8. 14(1H, d, J=7. 8Hz), 7. 82(1H, d, J=2. 0Hz), 7. 78(1H, d, J=7. 8Hz), 7. 69(1H, t, J=7. 8Hz), 7. 50(1H, dd, J=7. 8, 7. 3Hz), 7. 29(1H, dd, J=7. 8, 4. 9Hz), 3. 92(2H, s), 2. 37(3H, s)	208. 5-213. 7
157	1753, 1606, 1585, 1508, 1460, 746	DMSO-d6:9. 12(1H, s), 8. 65(1H, d, J=1. 5 Hz), 8. 38(1H, dd, J=4. 9, 1. 5Hz), 8. 34~8. 16(2H, m), 8. 07(1H, d, J=8. 3Hz), 7. 81~7. 40(4H, m), 7. 28(1H, dd, J=7. 8, 4. 9Hz), 5. 00(2H, s), 4. 21(2H, q, J=7. 1Hz), 3. 90(2H, s), 1. 24(3H, t, J=7. 1Hz)	256. 7 (decomposition)

Translator's note: Page 227 of the source text which includes the data for Example Nos. 158-163 is missing in the pdf copy of the patent available at the EPO and JPO and therefore has not been included.

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
164	1755, 1597, 1508, 1308, 1186, 787	DMSO-d6: 8. 95 (1H, s), 8. 37~8. 20 (2H, m), 8. 10~8. 07 (1H, m), 7. 64 (1H, dd, J=7. 8, 7. 3Hz), 7. 54 (1H, s), 7. 45 (1H, dd, J=7. 8, 7. 3Hz), 5. 02 (2H, s), 4. 21 (2H, q, J=6. 8Hz), 2. 12 (3H, s), 1. 24 (3H, t, J=6. 8Hz)	130. 9 (decomposition)
165	3500, 3080, 1734, 1566, 1475, 1308, 1215, 785	DMSO-d6: 13. 13 (1H, bs), 8. 96 (1H, s), 8. 29~8. 23 (2H, m), 8. 08 (1H, d, J=8. 3Hz), 7. 64 (1H, t, J=7. 3Hz), 7. 52 (1H, d, J=2. 0Hz), 7. 47~7. 42 (1H, m), 4. 92 (2H, s), 2. 13 (3H, s)	261. 0 (decomposition)
166	1649, 1603, 1512, 1466, 1304, 1018	DMSO-d6: 9. 33 (1H, s), 8. 60 (1H, s), 8. 31 (1H, d, J=7. 8Hz), 8. 25 (1H, d, J=2. 2Hz), 8. 15 (1H, d, J=7. 8Hz), 7. 93 (1H, s), 7. 68 (1H, dd, J=7. 8, 7. 3Hz), 7. 56 (1H, d, J=2. 2Hz), 7. 50 (1H, dd, J=7. 8, 7. 3Hz), 5. 34 (2H, s), 3. 96 (3H, s)	259. 7 (decomposition)
167	3300, 1572, 1508, 1458, 1398, 1304	DMSO-d6: 10. 17 (1H, s), 9. 28 (1H, s), 8. 60 (1H, s), 8. 25 (1H, d, J=7. 3Hz), 8. 12 (1H, d, J=8. 3Hz), 7. 98 (1H, d, J=2. 4Hz), 7. 93 (1H, s), 7. 67~7. 62 (1H, m), 7. 50~7. 44 (2H, m), 5. 31 (2H, s)	300. 0 (decomposition)
168	1749, 1649, 1612, 1506, 1234, 1223	DMSO-d6: 9. 40 (1H, s), 8. 62 (1H, s), 8. 61 (1H, s), 8. 30 (1H, d, J=7. 3Hz), 8. 18 (1H, d, J=8. 3Hz), 7. 94 (1H, s), 7. 84 (1H, s), 7. 75~7. 48 (2H, m), 5. 34 (2H, s), 2. 37 (3H, s)	224. 8 (decomposition)
169	3035, 1612, 1508, 1203, 1084, 816, 744	DMSO-d6: 8. 93 (1H, d, J=7. 6Hz), 8. 27 (1H, d, J=8. 1Hz), 8. 19 (1H, d, J=2. 2Hz), 8. 12 (1H, d, J=8. 1Hz), 7. 64 (1H, t, J=8. 1Hz), 7. 54 (1H, d, J=2. 2Hz), 7. 46 (1H, t, J=8. 1Hz), 6. 36 (1H, d, J=7. 6Hz), 3. 97 (3H, s)	226. 3-228. 4
170	1601, 1516, 1450, 1290, 818, 737	DMSO-d6: 10. 11 (1H, s), 8. 90 (1H, d, J=7. 6Hz), 8. 23 (1H, d, J=7. 3Hz), 8. 11 (1H, d, J=8. 3Hz), 7. 96 (1H, d, J=2. 0Hz), 7. 62 (1H, dd, J=8. 3, 7. 3Hz), 7. 47~7. 42 (2H, m), 6. 32 (1H, d, J=7. 6Hz)	276. 9 (decomposition)
171	1641, 1614, 1601, 1554, 1504, 1288, 818, 741	DMSO-d6: 9. 01 (1H, d, J=7. 8Hz), 8. 66 (1H, d, J=1. 7Hz), 8. 32 (1H, d, J=7. 6Hz), 8. 16 (1H, d, J=8. 1Hz), 8. 02 (1H, d, J=1. 7Hz), 7. 68 (1H, dd, J=8. 1, 7. 6Hz), 7. 50 (1H, dd, J=7. 6, 7. 6Hz), 6. 43 (1H, d, J=7. 8Hz)	264. 6-266. 2

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
172	3059, 2924, 1643, 1612, 1574, 1506, 1452, 1333	DMSO-d6: 9.04 (1H, s), 8.67 (1H, d, J=1.8 Hz), 8.34 (1H, d, J=7.8Hz), 8.13 (1H, d, J=8.3Hz), 8.07 (1H, d, J=1.8Hz), 7.69 (1H, dd, J=8.3, 7.3Hz), 7.49 (1H, dd, J=7.8, 7.3 Hz), 2.14 (3H, s)	278.8-281.0
173	2226, 1618, 1603, 1502, 1471, 1460, 820, 743	DMSO-d6: 9.09 (1H, d, J=7.6Hz), 9.05 (1H, s), 8.50 (1H, s), 8.38 (1H, d, J=8.3Hz), 8.22 (1H, d, J=8.3Hz), 7.77~7.71 (1H, m), 7.59~7.54 (1H, m), 6.52 (1H, d, J=7.6Hz)	300.0<
174	3342, 3200, 1664, 1593, 1504, 1288	DMSO-d6: 9.07~9.04 (2H, m), 8.70 (1H, s), 8.38~8.35 (2H, m), 8.19 (1H, d, J=8.3Hz), 7.69 (1H, t, J=7.8Hz), 7.64~7.45 (2H, m), 6.47 (1H, d, J=7.8Hz)	300.0<
175	1714, 1614, 1508, 1194, 1088	DMSO-d6: 13.35 (1H, bs), 9.09 (1H, s), 9.06 (1H, d, J=7.8Hz), 8.68 (1H, s), 8.45 (1H, d, J=7.8Hz), 8.19 (1H, d, J=8.3Hz), 7.72~7.49 (2H, m), 6.48 (1H, d, J=7.8Hz)	375.0<
176	1724, 1645, 1616, 1605, 1506, 1261, 766	DMSO-d6: 9.08~9.04 (2H, m), 8.67 (1H, d, J=1.5Hz), 8.46 (1H, d, J=7.3Hz), 8.19 (1H, d, J=8.3Hz), 7.74~7.68 (1H, m), 7.56~7.51 (1H, m), 6.49 (1H, d, J=7.8Hz), 4.00 (3H, s)	255.9 (decomposition)
177	1641, 1581, 1508, 1290, 1240, 746	DMSO-d6: 9.00 (1H, d, J=7.6Hz), 8.49 (1H, s), 8.30 (1H, d, J=7.3Hz), 8.16 (1H, d, J=8.3Hz), 8.09 (1H, s), 7.68~7.61 (1H, m), 7.48 (1H, dd, J=8.3, 7.3Hz), 6.41 (1H, d, J=7.6Hz), 5.53 (1H, t, J=5.7Hz), 4.81 (2H, d, J=5.7Hz),	164.3-169.3
178	1614, 1570, 1506, 1471, 1331, 798, 721	DMSO-d6: 9.24 (1H, s), 8.80 (1H, d, J=1.2 Hz), 8.70 (1H, s), 8.47 (1H, s), 8.34 (1H, d, J=7.7Hz), 8.16 (1H, d, J=1.2Hz), 8.12 (1H, d, J=7.7Hz), 7.94 (1H, d, J=7.7Hz), 7.71 (1H, t, J=7.7Hz), 7.51 (1H, t, J=7.7Hz), 7.48~7.37 (1H, m), 3.95 (2H, s)	274.7 (decomposition)
179	3365, 1643, 1560, 1514, 1466, 1313	DMSO-d6: 9.03 (1H, s), 8.63 (1H, s), 8.37 (1H, s), 8.14 (1H, d, J=7.3Hz), 8.09~8.01 (1H, m), 7.76 (1H, d, J=7.8Hz), 7.72 (1H, d, J=2.0Hz), 7.59 (1H, t, J=7.3Hz), 7.41 (1H, t, J=7.3Hz), 7.30~7.25 (2H, m), 5.62 (2H, s), 3.88 (2H, s)	246.5 (decomposition

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
180	1614, 1552, 1500, 1329, 816, 741	DMSO-d6:8. 99(1H, d, J=7. 3Hz), 8. 76(1H, d, J=2. 0Hz), 8. 30(1H, d, J=7. 3Hz), 8. 15~8. 13(1H, m), 8. 13(1H, d, J=2. 0Hz), 7. 67(1H, dd, J=8. 3, 7. 3Hz), 7. 49(1H, dd, J=7. 8, 7. 3Hz), 6. 42(1H, d, J=7. 3Hz)	294. 2 (decomposition)
181	3370, 1637, 1560, 1508, 1466, 1252, 824, 743	DMSO-d6:8. 82(1H, d, J=7. 8Hz), 8. 13(1H, d, J=7. 8Hz), 8. 07(1H, d, J=7. 8Hz), 7. 72(1H, d, J=2. 0Hz), 7. 61~7. 55(1H, m), 7. 45~7. 39(1H, m), 7. 28(1H, d, J=2. 0Hz), 6. 25(1H, d, J=7. 8Hz), 5. 64(2H, s)	182. 3-190. 3
182	3305, 1595, 1551, 1481, 1458, 1288, 808, 741	DMSO-d6:8. 82(1H, d, J=7. 6Hz), 8. 18(1H, d, J=7. 8Hz), 8. 07(1H, d, J=8. 3Hz), 7. 80(1H, s), 7. 59(1H, dd, J=7. 8, 7. 3Hz), 7. 45~7. 40(1H, m), 7. 16(1H, s), 6. 26(1H, d, J=7. 6Hz), 6. 20~6. 15(1H, m), 3. 20~3. 14(2H, m), 1. 71~1. 63(2H, m), 1. 01(3H, t, J=7. 3Hz)	145. 7 (decomposition)
183	3307, 3050, 1645, 1605, 1250, 816, 740	DMSO-d6:10. 42(1H, bs), 8. 97(1H, d, J=7. 8Hz), 8. 71(1H, d, J=2. 0Hz), 8. 31~8. 30(1H, m), 8. 25(1H, d, J=7. 8Hz), 8. 15(1H, d, J=8. 3Hz), 7. 68~7. 41(2H, m), 6. 37(1H, d, J=7. 8Hz), 2. 15(3H, s)	353. 8 (decomposition)
184	3433, 1645, 1597, 1576, 1504, 1448, 1329	DMSO-d6:9. 22(1H, s), 8. 64~8. 58(3H, m), 8. 39(1H, dd, J=4. 9, 1. 5Hz), 8. 17~8. 09(2H, m), 7. 87~7. 71(3H, m), 7. 29(1H, dd, J=7. 8, 4. 9Hz), 3. 91(2H, s)	278. 1 (decomposition)
185	2904, 1593, 1462, 1228, 1065, 758	DMSO-d6:9. 17(1H, s), 8. 65(1H, s), 8. 52(1H, d, J=7. 3Hz), 8. 38(1H, s), 8. 11(1H, d, J=7. 8Hz), 8. 04(1H, d, J=8. 8Hz), 7. 92(1H, d, J=2. 4Hz), 7. 78(1H, d, J=7. 8Hz), 7. 69(1H, dd, J=7. 8, 7. 3Hz), 7. 31~7. 23(2H, m), 3. 97~3. 85(5H, m)	210. 1 (decomposition)
186	3433, 3142, 3091, 1641, 1562, 1500, 1448, 1327	DMSO-d6:9. 74(1H, s), 9. 14(1H, s), 8. 70(1H, s), 8. 48~8. 45(2H, m), 8. 09(1H, d, J=7. 8Hz), 7. 95~7. 91(2H, m), 7. 66(1H, dd, J=7. 8, 7. 8Hz), 7. 62(1H, d, J=2. 2Hz), 7. 44~7. 40(1H, m), 7. 08(1H, dd, J=8. 8, 2. 2Hz), 3. 94(2H, s)	282. 4 (decomposition)
187	1645, 1618, 1510, 1452, 1323, 798	DMSO-d6:9. 02(1H, d, J=7. 8Hz), 8. 62~8. 59(2H, m), 8. 17~8. 14(2H, m), 7. 83(1H, dd, J=8. 5, 2. 2Hz), 7. 78~7. 72(1H, m), 6. 44(1H, d, J=7. 8Hz)	265. 5 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
188	3028, 1643, 1504, 1225, 1036, 810	DMSO-d6: 8. 95 (1H, d, J=7. 8Hz), 8. 53 (1H, d, J=7. 8Hz), 8. 11 (1H, d, J=7. 8Hz), 8. 06 (1H, d, J=9. 0Hz), 7. 91 (1H, d, J=2. 6Hz), 7. 70 (1H, t, J=7. 8Hz), 7. 23 (1H, dd, J=9. 0, 2. 6Hz), 6. 38 (1H, d, J=7. 8Hz), 3. 91 (3H, s)	175. 0 (decomposition)
189	3396, 3101, 1579, 1497, 1450, 1209, 1190	DMSO-d6: 8. 89 (1H, d, J=7. 8Hz), 8. 47 (1H, d, J=7. 6Hz), 8. 12 (1H, d, J=7. 8Hz), 7. 95 (1H, d, J=8. 8Hz), 7. 71 (1H, dd, J=7. 8, 7. 6Hz), 7. 63 (1H, d, J=2. 4Hz), 7. 07 (1H, dd, J=8. 8, 2. 4Hz), 6. 39 (1H, d, J=7. 8Hz)	290. 0 (decomposition)
190	3039, 1647, 1610, 1581, 1506, 1450, 1327	DMSO-d6: 9. 02 (1H, s), 8. 57 (1H, d, J=7. 6Hz), 8. 46 (1H, s), 8. 20~8. 13 (2H, m), 7. 75~7. 68 (2H, m), 2. 13 (3H, s)	296. 8-297. 7
191	3097, 1649, 1612, 1581, 1504, 1450, 1327, 783	DMSO-d6: 9. 39 (1H, s), 8. 63~8. 60 (2H, m), 8. 49 (1H, d, J=2. 0Hz), 8. 23~8. 16 (2H, m), 7. 93 (1H, s), 7. 80~7. 72 (2H, m), 5. 33 (2H, s)	293. 3-296. 9
192	1645, 1599, 1506, 1450, 1309	CDCl3: 8. 49 (1H, s), 8. 38 (1H, d, J=7. 8Hz), 8. 24 (1H, d, J=8. 3Hz), 8. 08 (1H, d, J=1. 8Hz), 7. 74~7. 62 (2H, m), 7. 55 (1H, dd, J=8. 3, 1. 8Hz), 3. 78 (4H, dd, J=4. 9, 4. 4Hz), 3. 67 (2H, s), 2. 65 (4H, dd, J=4. 9, 4. 4Hz)	231. 9-233. 8
193	3047, 1641, 1612, 1556, 1502, 1325, 798	DMSO-d6: 9. 02 (1H, d, J=7. 8Hz), 8. 60 (1H, d, J=7. 3Hz), 8. 48 (1H, d, J=2. 4Hz), 8. 21~8. 15 (2H, m), 7. 75~7. 72 (2H, m), 6. 44 (1H, d, J=7. 8Hz)	266. 6-269. 3
194	1668, 1608, 1504, 1333, 1228, 814	DMSO-d6: 9. 28 (1H, s), 8. 97 (1H, s), 8. 69~8. 66 (2H, m), 8. 40~8. 38 (1H, m), 8. 30~8. 21 (2H, m), 8. 15 (1H, d, J=7. 8Hz), 7. 81~7. 73 (2H, m), 7. 29 (1H, dd, J=7. 8, 4. 9Hz), 3. 93 (2H, s), 2. 74 (3H, s)	104. 3-106. 1
195	1647, 1614, 1506, 1335, 1257, 1230, 768	DMSO-d6: 13. 13 (1H, bs), 9. 27 (1H, s), 8. 92 (1H, s), 8. 70~8. 66 (2H, m), 8. 40~8. 39 (1H, m), 8. 27~8. 19 (2H, m), 8. 15 (1H, d, J=7. 6Hz), 7. 81~7. 78 (1H, m), 7. 74 (1H, t, J=7. 6Hz), 7. 30 (1H, dd, J=7. 6, 4. 6Hz), 3. 93 (2H, s)	300. 0<

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
196	1672, 1610, 1504, 1425, 1342, 1236, 762	DMSO-d6: 9. 18 (1H, s), 8. 93 (1H, s), 8. 63 (1H, d, J=7. 7Hz), 8. 27~8. 18 (2H, m), 8. 13 (1H, d, J=7. 7Hz), 7. 73 (1H, t, J=7. 7Hz), 7. 41 (2H, d, J=7. 3Hz), 7. 28 (2H, t, J=7. 3Hz), 7. 20~7. 14 (1H, m), 3. 91 (2H, s), 2. 73 (3H, s)	244. 5-245. 3
197	2926, 1707, 1560, 1506, 1246, 1223, 1176, 766	DMSO-d6: 13. 09 (1H, bs), 9. 17 (1H, s), 8. 89 (1H, s), 8. 64 (1H, d, J=7. 6Hz), 8. 25~8. 17 (2H, m), 8. 13 (1H, d, J=7. 6Hz), 7. 72 (1H, t, J=7. 6Hz), 7. 41 (2H, d, J=7. 3Hz), 7. 27 (2H, t, J=7. 3Hz), 7. 18 (1H, t, J=7. 3Hz), 3. 91 (2H, s)	278. 4 (decomposition)
198	2950, 2880, 1608, 1504, 1338, 1115, 764	CDCl3: 8. 78 (1H, d, J=1. 5Hz), 8. 41 (1H, d, J=7. 3Hz), 8. 34 (1H, d, J=7. 3Hz), 8. 29~8. 20 (1H, m), 8. 01 (1H, s), 7. 78~7. 66 (1H, m), 7. 62 (1H, d, J=8. 8Hz), 7. 45~7. 23 (5H, m), 4. 06 (2H, s), 3. 93 (2H, s), 3. 86~3. 83 (4H, m), 2. 73~2. 62 (4H, m)	amorphous
199	1643, 1583, 1568, 1508, 1325, 764	*DMSO-d6: 9. 14 (1H, s), 8. 53 (1H, d, J=7. 5Hz), 8. 30~8. 25 (1H, m), 8. 13~8. 06 (2H, m), 7. 70 (1H, t, J=7. 5Hz), 7. 63 (1H, d, J=8. 2Hz), 7. 40 (2H, d, J=7. 6Hz), 7. 27 (2H, t, J=7. 6Hz), 7. 16 (1H, t, J=7. 6Hz), 5. 38 (1H, d, J=3. 7Hz), 5. 00~4. 80 (1H, m), 3. 91 (2H, s), 1. 44 (3H, d, J=6. 6Hz)	145. 0-149. 0
200	1676, 1653, 1614, 1504, 1335, 1236, 795	DMSO-d6: 9. 03 (1H, d, J=7. 6Hz), 8. 92 (1H s), 8. 65 (1H, d, J=7. 6Hz), 8. 30~8. 23 (2H, m), 8. 14 (1H, d, J=7. 6Hz), 7. 75 (1H, t, J=7. 6Hz), 6. 46 (1H, d, J=7. 6Hz), 2. 73 (3H, s)	263. 3 (decomposition)
201	1701, 1589, 1508, 1219, 1188, 768	DMSO-d6: 13. 11 (1H, bs), 9. 07 (1H, d, J=7. 8Hz), 8. 93 (1H, s), 8. 71 (1H, d, J=7. 6Hz), 8. 25~8. 24 (2H, m), 8. 16 (1H, d, J=7. 6Hz), 7. 76 (1H, t, J=7. 6Hz), 6. 47 (1H, d, J=7. 8Hz)	360. 0<
202	1686, 1643, 1610, 1502, 1294, 1194, 1107	CDCl3: 8. 79 (1H, d, J=1. 0Hz), 8. 37~8. 28 (4H, m), 7. 77~7. 69 (2H, m), 6. 59 (1H, d, J=7. 8Hz), 3. 96 (2H, s), 3. 81 (4H, t, J=4. 6Hz), 2. 69 (4H, t, J=4. 6Hz)	188. 1-194. 0

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
203	2950, 1643, 1593, 1458, 1271, 789, 716	*DMSO-d6: 9. 18 (1H, s), 8. 64 (1H, d, J=1. 7Hz), 8. 38 (1H, d, J=4. 7. 1. 7Hz), 8. 16~8. 12 (3H, m), 7. 78 (1H, d, J=7. 8Hz), 7. 63 (1H, t, J=7. 9), 7. 47 (1H, t, J=7. 9Hz), 7. 40 (1H, d, J=9. 0Hz), 7. 28 (1H, dd, J=7. 8, 4. 7Hz), 4. 18 (3H, s), 3. 90 (2H, s)	207. 2 (decomposition)
204	1643, 1560, 1525, 1446, 1321, 1281, 750	DMSO-d6: 11. 64 (1H, bs), 9. 14 (1H, s), 8. 63 (1H, s), 8. 46~8. 35 (1H, m), 8. 17~8. 10 (2H, m), 7. 99 (1H, d, J=8. 8Hz), 7. 86~7. 72 (1H, m), 7. 59 (1H, t, J=7. 1Hz), 7. 46 (1H, t, J=7. 1Hz), 7. 28 (1H, dd, J=7. 6, 4. 6Hz), 7. 15 (1H, d, J=8. 8Hz), 3. 89 (2H, s)	339. 7 (decomposition)
205	1759, 1649, 1612, 1458, 1329, 1192, 754	DMSO-d6: 9. 23 (1H, s), 8. 65 (1H, d, J=2. 0Hz), 8. 40~8. 38 (1H, m), 8. 20~8. 12 (2H, m), 8. 04 (1H, d, J=7. 6Hz), 7. 78 (1H, dt, J=7. 8, 2. 0Hz), 7. 69 (1H, t, J=7. 6Hz), 7. 53~7. 47 (2H, m), 7. 29 (1H, dd, J=7. 8, 3. 9Hz), 3. 92 (2H, s), 2. 58 (3H, s)	247. 8 (decomposition)
206	1645, 1587, 1581, 1460, 1296, 1207, 1111	DMSO-d6: 9. 18 (1H, s), 8. 64 (1H, s), 8. 38 (1H, d, J=4. 4Hz), 8. 24 (1H, d, J=7. 3Hz), 8. 15~8. 08 (2H, m), 7. 78 (1H, d, J=7. 3Hz), 7. 64 (1H, dd, J=7. 8, 7. 3Hz), 7. 50 (1H, dd, J=7. 8, 7. 3Hz), 7. 32~7. 25 (2H, m), 5. 23 (2H, s), 4. 24 (2H, q, J=7. 0Hz), 3. 91 (2H, s), 1. 26 (3H, t, J=7. 0Hz)	231. 5 (decomposition)
207	3050, 1639, 1593, 1460, 1261, 789	DMSO-d6: 8. 92 (1H, d, J=7. 8Hz), 8. 12~8. 09 (3H, m), 7. 58 (1H, t, J=8. 3Hz), 7. 45 (1H, t, J=8. 3Hz), 7. 36 (1H, d, J=8. 8Hz), 6. 34 (1H, d, J=7. 8Hz), 4. 17 (3H, s)	210. 8 (decomposition)
208	1632, 1568, 1446, 1308, 1186, 810	DMSO-d6: 11. 66 (1H, s), 8. 93 (1H, d, J=7. . 8Hz), 8. 20~8. 12 (2H, m), 8. 01 (1H, d, J=8. 8Hz), 7. 61~7. 42 (2H, m), 7. 16 (1H, d, J=8. 3Hz), 6. 34 (1H, d, J=7. 8Hz)	360. 0 (decomposition)
209	1759, 1651, 1616, 1458, 1194, 746	*DMSO-d6: 9. 03 (1H, d, J=7. 8Hz), 8. 21~8. 14 (2H, m), 8. 05 (1H, d, J=7. 6Hz), 7. 69 (1H, t, J=7. 6Hz), 7. 53~7. 47 (2H, m), 6. 44 (1H, d, J=7. 8Hz), 2. 59 (3H, s)	239. 6 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
210	1643, 1595, 1570, 1508, 1470, 1338, 1273	*DMSO-d6: 9. 17 (1H, s), 8. 63 (1H, d, J=1. 5Hz), 8. 45 (1H, d, J=8. 3Hz), 8. 37 (1H, dd, J=4. 7, 1. 7Hz), 8. 21 (1H, d, J=7. 4Hz), 8. 09 (1H, d, J=8. 2Hz), 7. 76 (1H, ddd, J=8. 0, 1. 7, 1. 5Hz), 7. 57 (1H, dd, J=8. 2, 7. 4Hz), 7. 44 (1H, dd, J=7. 4, 7. 4Hz), 7. 27 (1H, dd, J=8. 0, 4. 7Hz), 7. 23 (1H, d, J=8. 3Hz), 3. 96 (3H, s), 3. 86 (2H, s)	215. 1 (decomposition)
211	1664, 1560, 1504, 1464, 1273, 760	DMSO-d6: 12. 04 (1H, s), 9. 39 (1H, s), 8. 66 (1H, s), 8. 43～8. 40 (2H, m), 8. 25～8. 12 (2H, m), 7. 80 (1H, d, J=7. 8Hz), 7. 63～7. 54 (1H, m), 7. 49 (1H, t, J=7. 3Hz), 7. 31 (1H, dd, J=7. 8, 4. 9Hz), 7. 04 (1H, d, J=8. 3Hz), 3. 98 (2H, s)	236. 2 (decomposition)
212	1759, 1645, 1614, 1508, 1456, 1213, 760	DMSO-d6: 9. 23 (1H, s), 8. 62 (1H, s), 8. 54 (1H, d, J=7. 8Hz), 8. 39 (1H, d, J=4. 9Hz), 8. 30 (1H, d, J=7. 8Hz), 8. 15 (1H, d, J=8. 3Hz), 7. 75 (1H, d, J=7. 8Hz), 7. 73～7. 62 (1H, m), 7. 58～7. 44 (1H, m), 7. 35 (1H, d, J=8. 3Hz), 7. 29 (1H, dd, J=7. 8, 4. 9Hz), 3. 89 (2H, s), 2. 37 (3H, s)	240. 2 (decomposition)
213	1637, 1578, 1506, 1466, 1261	DMSO-d6: 8. 90 (1H, d, J=7. 6Hz), 8. 44 (1H, d, J=8. 3Hz), 8. 19 (1H, d, J=7. 8Hz), 8. 10 (1H, d, J=8. 3Hz), 7. 57～7. 51 (1H, m), 7. 46～7. 40 (1H, m), 7. 24 (1H, d, J=8. 3Hz), 6. 32 (1H, d, J=7. 6Hz), 3. 98 (3H, s)	57. 3-60. 6
214	1664, 1491, 1468, 1265, 1219, 829, 733	DMSO-d6: 12. 13 (1H, s), 9. 20 (1H, d, J=7. 8Hz), 8. 43 (1H, d, J=8. 3Hz), 8. 21 (2H, d, J=8. 3Hz), 7. 60～7. 47 (2H, m), 7. 07 (1H, d, J=8. 3Hz), 6. 57 (1H, d, J=7. 8Hz)	238. 2 (decomposition)
215	1761, 1639, 1612, 1504, 1454, 1190, 1026, 744	DMSO-d6: 9. 03 (1H, d, J=7. 8Hz), 8. 56 (1H, d, J=8. 3Hz), 8. 31 (1H, d, J=7. 8Hz), 8. 18 (1H, d, J=7. 8Hz), 7. 69～7. 46 (2H, m), 7. 37 (1H, d, J=8. 3Hz), 6. 36 (1H, d, J=7. 8Hz), 2. 38 (3H, s)	178. 1 (decomposition)
216	1643, 1572, 1460, 1286, 1246, 1055, 748	*DMSO-d6: 8. 98 (1H, s), 8. 62 (1H, d, J=1. 7Hz), 8. 51 (1H, d, J=7. 6Hz), 8. 41 (1H, dd, J=4. 6, 1. 7Hz), 8. 14 (1H, d, J=7. 9Hz), 7. 88 (1H, d, J=7. 6Hz), 7. 78～7. 75 (1H, m), 7. 71 (1H, t, J=7. 6Hz), 7. 43 (1H, t, J=7. 9Hz), 7. 33～7. 29 (2H, m), 4. 06 (3H, s), 3. 95 (2H, s)	214. 1-216. 3

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
217	1641, 1558, 1458, 1329, 1286, 764	*DMSO-d6:10. 87 (1H, s), 8. 97 (1H, s), 8. 61 (1H, d, J=1. 7Hz), 8. 48 (1H, d, J=7. 7Hz), 8. 41 (1H, dd, J=4. 9, 1. 7Hz), 8. 14 (1H, d, J=7. 6Hz), 7. 77~7. 73 (2H, m), 7. 70 (1H, t, J=7. 7Hz), 7. 32~7. 26 (2H, m), 7. 08 (1H, d, J=7. 6Hz), 3. 95 (2H, s)	300. 0 (decomposition)
218	1770, 1599, 1572, 1431, 1186, 1146, 760	*DMSO-d6:8. 66~8. 62 (1H, m), 8. 58 (1H, d, J=7. 5Hz), 8. 45 (1H, dd, J=4. 7, 1. 5Hz), 8. 42 (1H, s), 8. 22~8. 17 (2H, m), 7. 80~7. 73 (2H, m), 7. 51~7. 45 (2H, m), 7. 36 (1H, dd, J=7. 8, 4. 7Hz), 3. 97 (2H, s), 2. 35 (3H, s)	180. 0-183. 6
219	1751, 1593, 1566, 1431, 1335, 1215, 762	*DMSO-d6:9. 30 (1H, s), 8. 61 (1H, s), 8. 55 (1H, d, J=7. 3Hz), 8. 39~8. 38 (1H, m), 8. 16 (1H, d, J=8. 0Hz), 7. 95 (1H, d, J=7. 3Hz), 7. 76~7. 71 (2H, m), 7. 42 (1H, t, J=8. 0Hz), 7. 36~7. 25 (2H, m), 5. 14 (2H, s), 4. 24 (2H, q, J=7. 2Hz), 3. 93 (2H, s), 1. 23 (3H, t, J=7. 2Hz)	248. 1 (decomposition)
220	1641, 1618, 1497, 1454, 1284, 1188, 1016, 770	*DMSO-d6:8. 96 (1H, d, J=7. 9Hz), 8. 54 (1H, d, J=7. 7Hz), 8. 13 (1H, d, J=7. 8Hz), 7. 90 (1H, d, J=7. 7Hz), 7. 73 (1H, d, J=7. 7Hz), 7. 45 (1H, d, J=7. 8Hz), 7. 33 (1H, d, J=7. 8Hz), 6. 38 (1H, d, J=7. 9Hz), 4. 10 (3H, s)	230. 4-232. 7
221	1639, 1560, 1502, 1456, 1292, 1188, 775	*DMSO-d6:10. 95 (1H, s), 8. 97 (1H, d, J=7. 7Hz), 8. 49 (1H, d, J=7. 7Hz), 8. 12 (1H, d, J=7. 7Hz), 7. 77~7. 68 (2H, m), 7. 30 (1H, t, J=7. 9Hz), 7. 10 (1H, d, J=7. 9Hz), 6. 37 (1H, d, J=7. 7Hz)	300. 0 (decomposition)
222	1767, 1649, 1626, 1458, 1435, 1184, 771	*DMSO-d6:8. 70 (1H, d, J=7. 9Hz), 8. 59 (1H, d, J=7. 7Hz), 8. 22 (1H, dd, J=6. 0, 3. 0Hz), 8. 16 (1H, d, J=7. 7Hz), 7. 76 (1H, t, J=7. 7Hz), 7. 52~7. 50 (2H, m), 6. 39 (1H, d, J=7. 9Hz), 2. 09 (3H, s)	210. 1-212. 4
223	1749, 1643, 1622, 1497, 1458, 1234, 773	*DMSO-d6:9. 12 (1H, d, J=7. 9Hz), 8. 54 (1H, d, J=7. 6Hz), 8. 14 (1H, d, J=7. 9Hz), 7. 93 (1H, d, J=7. 6Hz), 7. 73 (1H, t, J=7. 6Hz), 7. 44~7. 39 (1H, m), 7. 30 (1H, d, J=8. 1Hz), 6. 40 (1H, d, J=7. 9Hz), 5. 13 (2H, s), 4. 24 (2H, q, J=7. 2Hz), 1. 26 (3H, t, J=7. 2Hz)	200. 2-202. 6

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
224	1624, 1612, 1514, 1470, 1244, 756	DMSO-d6: 9. 24 (1H, s), 8. 65 (1H, d, J=1. 5 Hz), 8. 40~8. 37 (2H, m), 8. 17 (1H, d, J=8. 5Hz), 8. 01 (1H, d, J=7. 6Hz), 7. 81 (1H, d, J =2. 3Hz), 7. 80~7. 75 (1H, m), 7. 65 (1H, t, J=7. 6Hz), 7. 31~7. 27 (1H, m), 7. 07 (1H, dd, J=8. 5, 2. 3Hz), 3. 95 (3H, s), 3. 91 (2H, s)	207. 2 (decomposition)
225	3050, 1614, 1498, 1448, 1279, 1232, 827	DMSO-d6: 10. 25 (1H, bs), 9. 11 (1H, s), 8. 64 (1H, d, J=2. 0Hz), 8. 41~8. 28 (2H, m), 8. 05 (1H, d, J=8. 4Hz), 7. 97 (1H, dd, J=7. 8, 1. 0Hz), 7. 82~7. 74 (1H, m), 7. 62 (1H, t, J =7. 8Hz), 7. 47 (1H, d, J=2. 1Hz), 7. 32~7. 25 (1H, m), 6. 92 (1H, dd, J=8. 4, 2. 1Hz), 3. 90 (2H, s)	335. 0 (decomposition)
226	1755, 1647, 1616, 1510, 1444, 1215, 762	DMSO-d6: 9. 17 (1H, s), 8. 64 (1H, s), 8. 53 (1H, d, J=7. 7Hz), 8. 40~8. 38 (1H, m), 8. 33, (1H, d, J=8. 3Hz), 8. 11 (1H, d, J=7. 7Hz), 8. 02 (1H, d, J=2. 0Hz), 7. 79~7. 68 (2H, m), 7. 31~7. 25 (2H, m), 3. 90 (2H, s), 2. 38 (3H, s)	223. 1 (decomposition)
227	1751, 1610, 1514, 1468, 1230, 1200	DMSO-d6: 9. 20 (1H, s), 8. 63 (1H, d, J=1. 5 Hz), 8. 42~8. 37 (2H, m), 8. 18 (1H, d, J=8. 5Hz), 8. 01 (1H, d, J=7. 8Hz), 7. 85 (1H, d, J =2. 3Hz), 7. 76 (1H, d, J=7. 8Hz), 7. 66 (1H, t, J=7. 8Hz), 7. 28 (1H, dd, J=7. 8, 4. 9Hz), 7. 09 (1H, dd, J=8. 5, 2. 3Hz), 4. 97 (2H, s), 4. 22 (2H, q, J=7. 0Hz), 3. 91 (2H, s), 1. 25 (3H, t, J=7. 0Hz)	128. 3-133. 0
228	3080, 3020, 2825, 1649, 1614, 1516, 1232, 791	*DMSO-d6: 9. 02 (1H, d, J=7. 7Hz), 8. 40 (1H, d, J=7. 5Hz), 8. 17 (1H, d, J=8. 7Hz), 8. 01 (1H, d, J=7. 5Hz), 7. 85 (1H, d, J=2. 3Hz), 7. 66 (1H, t, J=7. 5Hz), 7. 07 (1H, dd, J=8. 7, 2. 3Hz), 6. 42 (1H, d, J=7. 7Hz), 3. 93 (3H, s)	254. 5 (decomposition)
229	1628, 1587, 1448, 1215, 797	DMSO-d6: 10. 19 (1H, s), 8. 91 (1H, d, J=7. 8Hz), 8. 33 (1H, d, J=7. 3Hz), 8. 06~7. 96 (2H, m), 7. 63 (1H, dd, J=7. 8, 7. 8Hz), 7. 49 (1H, d, J=2. 0Hz), 6. 94~6. 90 (1H, m), 6. 36 (1H, d, J=7. 3Hz)	375. 0 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
230	3053, 1751, 1614, 1508, 1194, 1161, 767	DMSO-d6: 8. 96 (1H, d, J=7. 8Hz), 8. 53 (1H, d, J=7. 6Hz), 8. 33 (1H, d, J=8. 6Hz), 8. 11 (1H, d, J=7. 6Hz), 8. 06 (1H, d, J=2. 1Hz), 7. 73 (1H, t, J=7. 6Hz), 7. 27 (1H, dd, J=8. 6, 2. 1Hz), 6. 43 (1H, d, J=7. 8Hz), 2. 37 (3H, s)	257. 2 (decomposition)
231	1759, 1614, 1514, 1209, 1196, 1097, 793	DMSO-d6: 8. 98 (1H, d, J=7. 8Hz), 8. 41 (1H, d, J=7. 8Hz), 8. 17 (1H, d, J=8. 6Hz), 8. 02 (1H, d, J=7. 8Hz), 7. 88 (1H, d, J=2. 3Hz), 7. 67 (1H, t, J=7. 8Hz), 7. 09 (1H, dd, J=8. 6, 2. 3Hz), 6. 42 (1H, d, J=7. 8Hz), 4. 95 (2H, s), 4. 22 (2H, q, J=7. 2Hz), 1. 25 (3H, t, J=7. 2Hz)	163. 1-168. 6
232	1608, 1572, 1487, 1458, 1267, 1078, 779	DMSO-d6: 9. 16 (1H, s), 8. 63 (1H, d, J=2. 4Hz), 8. 37 (1H, dd, J=4. 6, 1. 5Hz), 8. 31 (1H, d, J=7. 8Hz), 8. 04 (1H, d, J=7. 8Hz), 7. 79~7. 75 (1H, m), 7. 75~7. 53 (3H, m), 7. 27 (1H, dd, J=7. 8, 4. 6Hz), 7. 06 (1H, d, J=7. 8Hz), 4. 06 (3H, s), 3. 89 (2H, s)	218. 8 (decomposition)
233	2981, 1597, 1574, 1483, 1454, 1284, 748	DMSO-d6: 10. 79 (1H, bs), 9. 17 (1H, s), 8. 65 (1H, s), 8. 39~8. 32 (2H, m), 8. 04 (1H, d, J=7. 7Hz), 7. 78 (1H, d, J=7. 6Hz), 7. 66 (1H, t, J=7. 7Hz), 7. 56 (1H, d, J=8. 1Hz), 7. 46 (1H, t, J=8. 1Hz), 7. 28 (1H, dd, J=7. 6, 4. 6Hz), 6. 91 (1H, d, J=8. 1Hz), 3. 91 (2H, s)	295. 6 (decomposition)
234	1755, 1614, 1462, 1227, 1200, 754	DMSO-d6: 9. 24 (1H, s), 8. 65 (1H, d, J=2. 0Hz), 8. 39 (1H, dd, J=4. 9, 1. 5Hz), 8. 28 (1H, d, J=7. 9Hz), 8. 14 (1H, d, J=7. 9Hz), 8. 05 (1H, d, J=7. 9Hz), 7. 78 (1H, dd, J=7. 8, 2. 0Hz), 7. 70 (2H, t, J=7. 9Hz), 7. 31~7. 26 (2H, m), 3. 92 (2H, s), 2. 51 (3H, s)	217. 3 (decomposition)
235	1605, 1570, 1508, 1485, 1464, 1279, 1146	DMSO-d6: 9. 14 (1H, s), 8. 63 (1H, d, J=2. 0Hz), 8. 38 (1H, dd, J=5. 0, 1. 5Hz), 8. 23 (1H, d, J=2. 4Hz), 8. 22~8. 08 (2H, m), 7. 78~7. 74 (1H, m), 7. 58 (1H, d, J=2. 4Hz), 7. 53 (1H, ddd, J=9. 0, 9. 0, 2. 5Hz), 7. 28 (1H, dd, J=7. 6, 5. 0Hz), 3. 95 (3H, s), 3. 90 (2H, s)	251. 4-255. 7

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
236	1583, 1576, 1564, 1508, 1471, 1389, 1335	DMSO-d6: 10. 10 (1H, s), 9. 11 (1H, s), 8. 64 (1H, s), 8. 40~8. 39 (1H, m), 8. 17 (1H, dd, J=8. 8, 2. 4Hz), 8. 10 (1H, dd, J=9. 0, 4. 1Hz), 7. 99 (1H, d, J=2. 2Hz), 7. 80 (1H, d, J=7. 8Hz), 7. 54~7. 46 (2H, m), 7. 50 (1H, d, J=2. 2Hz), 7. 31 (1H, dd, J=7. 8, 4. 9Hz), 3. 89 (2H, s)	306. 2 (decomposition)
237	1605, 1574, 1508, 1483, 1336, 1196, 1186	DMSO-d6: 9. 22 (1H, s), 8. 64 (1H, s), 8. 41~8. 37 (2H, m), 8. 21~8. 14 (2H, m), 7. 87 (1H, d, J=2. 0Hz), 7. 79~7. 75 (1H, m), 7. 57 (1H, ddd, J=9. 3, 9. 3, 2. 4Hz), 7. 29 (1H, dd, J=7. 6, 4. 6Hz), 3. 91 (2H, s), 2. 37 (3H, s)	226. 8 (decomposition)
238	2970, 1751, 1481, 1333, 1200, 1142	DMSO-d6: 9. 23 (1H, s), 8. 64 (1H, d, J=2. 0Hz), 8. 40~8. 38 (2H, m), 8. 27~8. 13 (2H, m), 7. 85 (1H, d, J=2. 0Hz), 7. 78 (1H, dd, J=5. 9, 2. 0Hz), 7. 58 (1H, ddd, J=11. 7, 8. 8, 2. 4Hz), 7. 29 (1H, dd, J=7. 6, 4. 7Hz), 3. 91 (2H, s), 2. 68 (2H, t, J=7. 3Hz), 1. 80~1. 65 (2H, m), 1. 03 (3H, t, J=7. 3Hz)	221. 1-217. 1
239	1649, 1593, 1556, 1506, 1485, 1462, 1275	DMSO-d6: 8. 90 (1H, d, J=7. 6Hz), 8. 20 (1H, d, J=2. 2Hz), 8. 17~8. 02 (2H, m), 7. 56 (1H, d, J=2. 2Hz), 7. 54~7. 46 (1H, m), 6. 34 (1H, d, J=7. 6Hz), 3. 96 (3H, s)	233. 3-239. 1
240	1655, 1603, 1477, 1437, 1402, 1277, 1194	DMSO-d6: 10. 20 (1H, s), 8. 89 (1H, d, J=7. 8Hz), 8. 17~8. 11 (2H, m), 7. 99 (1H, d, J=2. 4Hz), 7. 53~7. 41 (2H, m), 6. 31 (1H, d, J=7. 8Hz)	360. 0<
241	1761, 1593, 1500, 1190, 841	DMSO-d6: 9. 01 (1H, d, J=7. 6Hz), 8. 39 (1H, d, J=2. 0Hz), 8. 23~8. 17 (2H, m), 7. 88 (1H, d, J=2. 0Hz), 7. 60~7. 52 (1H, m), 6. 42 (1H, d, J=7. 6Hz), 2. 39 (3H, s)	267. 8 (decomposition)
242	1751, 1597, 1504, 1487, 1273, 1194, 1151	DMSO-d6: 9. 02 (1H, d, J=7. 8Hz), 8. 40 (1H, d, J=2. 0Hz), 8. 24~8. 19 (2H, m), 7. 85 (1H, d, J=2. 0Hz), 7. 56 (1H, ddd, J=9. 3, 9. 3, 2. 4Hz), 6. 42 (1H, d, J=7. 8Hz), 2. 68 (2H, t, J=7. 3Hz), 1. 73 (2H, qt, J=7. 3, 7. 3Hz), 1. 04 (3H, t, J=7. 3Hz)	194. 5 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
243	1608, 1579, 1506, 1477, 1433, 1423, 1333	DMSO-d6:9. 14(1H, s), 8. 63(1H, d, J=0. 8 Hz), 8. 44(1H, d, J=1. 0Hz), 8. 38(1H, d, J=4. 9Hz), 8. 26(1H, d, J=1. 0Hz), 8. 11(1H, d, J=8. 3Hz), 7. 81~7. 74(1H, m), 7. 71(1H, dd, J=8. 2, 0. 8Hz), 7. 58(1H, d, J=1. 0Hz), 7. 28(1H, dd, J=8. 2, 4. 9Hz), 3. 95(3H, s), 3. 90(2H, s)	221. 7-225. 6
244	3317, 1581, 1510, 1454, 1425, 1392, 1331	DMSO-d6:10. 15(1H, s), 9. 12(1H, s), 8. 68(1H, s), 8. 47~8. 36(2H, m), 8. 10(1H, d, J=8. 8Hz), 8. 02(1H, s), 7. 88(1H, d, J=7. 6Hz), 7. 72~7. 64(1H, m), 7. 54~7. 48(1H, m), 7. 39(1H, dd, J=7. 6, 4. 4Hz), 3. 91(2H, s)	300. 0<
245	1751, 1606, 1581, 1504, 1477, 1331, 1192	DMSO-d6:9. 16(1H, s), 8. 63(1H, d, J=2. 4Hz), 8. 46(1H, d, J=2. 0Hz), 8. 38(1H, dd, J=4. 7, 1. 8Hz), 8. 34(1H, d, J=2. 4Hz), 8. 13(1H, d, J=8. 8Hz), 7. 78~7. 70(2H, m), 7. 56(1H, d, J=2. 4Hz), 7. 30~7. 25(1H, m), 5. 01(2H, s), 4. 20(2H, q, J=7. 3Hz), 3. 90(2H, s), 1. 23(3H, t, J=7. 3Hz)	194. 4-197. 1
246	3061, 1653, 1606, 1556, 1504, 1475, 1325, 814	DMSO-d6:8. 94(1H, d, J=8. 1Hz), 8. 44(1H, d, J=1. 8Hz), 8. 28(1H, d, J=1. 8Hz), 8. 16(1H, d, J=8. 6Hz), 7. 70(1H, dd, J=8. 6, 1. 8Hz), 7. 59(1H, d, J=1. 8Hz), 6. 38(1H, d, J=8. 1Hz), 3. 96(3H, s)	261. 3-263. 6
247	3078, 1651, 1601, 1508, 1454, 1429, 1400, 1327, 1190	DMSO-d6:10. 18(1H, bs), 8. 91(1H, d, J=7. 8Hz), 8. 41(1H, s), 8. 14(1H, d, J=8. 8Hz), 8. 02(1H, d, J=2. 0Hz), 7. 66(1H, d, J=8. 8Hz), 7. 49(1H, d, J=2. 0Hz), 6. 33(1H, d, J=7. 8Hz)	300. 0<
248	2966, 1597, 1570, 1508, 1452, 1333	*DMSO-d6:9. 12(1H, s), 8. 64(1H, s), 8. 38(1H, d, J=4. 7Hz), 8. 17(1H, d, J=2. 2Hz), 8. 13(1H, s), 8. 00(1H, d, J=8. 3Hz), 7. 78~7. 75(1H, m), 7. 53~7. 49(2H, m), 7. 28(1H, dd, J=7. 9, 4. 7Hz), 3. 95(3H, s), 3. 90(2H, s), 2. 80(2H, q, J=7. 7Hz), 1. 30(3H, t, J=7. 7Hz)	143. 1-144. 6

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
249	3446, 1605, 1504, 1433, 1325	*DMSO-d6: 10.06 (1H, s), 9.08 (1H, s), 8.62 (1H, s), 8.38~8.37 (1H, m), 8.08 (1H, s), 7.98 (1H, d, J=8.4Hz), 7.92 (1H, d, J=2.0Hz), 7.74~7.70 (1H, m), 7.48 (1H, dd, J=8.4, 1.6Hz), 7.44 (1H, d, J=2.0Hz), 7.28 (1H, dd, J=8.0, 4.9Hz), 3.88 (2H, s), 2.81~2.78 (2H, m), 1.29 (3H, t, J=7.5Hz)	247.0-249.4
250	1755, 1605, 1587, 1566, 1504, 1323, 1198	*DMSO-d6: 9.13 (1H, s), 8.63 (1H, d, J=1.7Hz), 8.37 (1H, dd, J=4.9, 1.7Hz), 8.24 (1H, d, J=2.3Hz), 8.14 (1H, s), 8.00 (1H, d, J=8.3Hz), 7.77 (1H, d, J=8.0Hz), 7.53~7.49 (1H, m), 7.49 (1H, d, J=2.2Hz), 7.28 (1H, dd, J=8.0, 4.9Hz), 5.01 (2H, s), 4.20 (2H, q, J=7.2Hz), 3.90 (2H, s), 2.80 (2H, q, J=7.6Hz), 1.30 (3H, t, J=7.6Hz), 1.23 (3H, t, J=7.2Hz)	146.7-147.5
251	1585, 1566, 1508, 1483, 1327, 1234, 714	*DMSO-d6: 9.13 (1H, s), 8.76 (1H, d, J=2.0Hz), 8.64 (1H, d, J=2.1Hz), 8.57 (1H, dd, J=5.0, 2.0Hz), 8.38 (1H, dd, J=5.0, 2.1Hz), 8.30 (1H, d, J=2.2Hz), 8.13 (1H, d, J=1.6Hz), 8.01 (1H, d, J=8.3Hz), 7.95 (1H, d, J=8.0Hz), 7.77 (1H, d, J=8.0Hz), 7.66 (1H, d, J=2.2Hz), 7.52 (1H, dd, J=8.3, 1.6Hz), 7.47 (1H, dd, J=8.0, 5.0Hz), 7.28 (1H, d, J=8.0, 5.0Hz), 5.38 (2H, s), 3.90 (2H, s), 2.80 (2H, q, J=7.6Hz), 1.30 (3H, t, J=7.6Hz)	163.0-163.4
252	3010, 1589, 1568, 1510, 1489, 1147, 700	DMSO-d6: 9.09 (1H, s), 8.63 (1H, d, J=2.0Hz), 8.38~8.36 (1H, m), 8.31 (1H, d, J=2.0Hz), 8.00 (1H, d, J=9.3Hz), 7.90 (1H, d, J=2.4Hz), 7.78~7.74 (1H, m), 7.63 (1H, d, J=2.0Hz), 7.54~7.51 (2H, m), 7.45~7.22 (5H, m), 5.32 (2H, s), 3.90~3.89 (5H, m)	192.7-196.4
253	1560, 1485, 1284, 1211, 839	DMSO-d6: 10.08 (1H, bs), 9.05 (1H, s), 8.66~8.58 (1H, m), 8.37 (1H, dd, J=4.9, 1.5Hz), 8.00~7.95 (2H, m), 7.86 (1H, d, J=2.4Hz), 7.77~7.73 (1H, m), 7.46 (1H, d, J=2.4Hz), 7.27 (1H, dd, J=7.8, 4.9Hz), 7.21 (1H, dd, J=8.8, 2.4Hz), 3.93~3.81 (5H, m)	287.7 (decomposition)

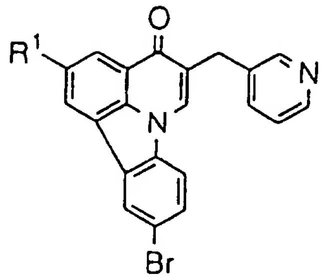
Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
254	1724, 1605, 1508, 1308, 1205, 1028	DMSO-d6: 9.10 (1H, s), 8.63 (1H, s), 8.38 ~8.37 (1H, m), 8.28 (1H, d, J=2.4Hz), 8.01 (1H, d, J=8.8Hz), 7.92 (1H, d, J=2.4Hz), 7.76 (1H, d, J=7.8Hz), 7.51 (1H, d, J=2.4Hz), 7.29~7.23 (2H, m), 5.00 (2H, s), 4.21 (2H, q, J=7.2Hz), 3.90 (3H, s), 3.89 (2H, s), 1.23 (3H, t, J=7.2Hz)	178.7-182.7
255	3002, 1608, 1589, 1508, 1485, 1282, 1217, 816	DMSO-d6: 8.86 (1H, d, J=7.6Hz), 8.30 (1H, d, J=2.0Hz), 8.02 (1H, d, J=8.8Hz), 7.88 (1H, d, J=2.7Hz), 7.63~7.32 (6H, m), 7.21 (1H, dd, J=8.8, 2.7Hz), 6.30 (1H, d, J=7.6Hz), 5.33 (2H, s), 3.90 (3H, s)	159.4 (decomposition)
256	1585, 1485, 1450, 1281, 825	DMSO-d6: 10.08 (1H, s), 8.83 (1H, d, J=7.8Hz), 8.01 (1H, d, J=8.8Hz), 7.96 (1H, d, J=2.4Hz), 7.85 (1H, d, J=2.4Hz), 7.49~7.42 (1H, m), 7.20 (1H, dd, J=8.8, 2.4Hz), 6.26 (1H, d, J=7.8Hz), 3.89 (3H, s)	328.6 (decomposition)
257	2950, 1585, 1466, 1288, 1213, 1034, 789	DMSO-d6: 9.04 (1H, s), 8.64 (1H, s), 8.38 (1H, d, J=1.5Hz), 8.15 (1H, d, J=1.5Hz), 7.96 (1H, d, J=8.8Hz), 7.86 (1H, d, J=2.0Hz), 7.77 (1H, d, J=7.3Hz), 7.51 (1H, d, J=1.5Hz), 7.30~7.19 (2H, m), 4.02~3.78 (8H, m)	206.3 (decomposition)
258	3103, 1558, 1497, 1448, 1327, 1201, 1151	DMSO-d6: 10.17 (1H, s), 9.85 (1H, s), 9.05 (1H, s), 8.63 (1H, d, J=1.5Hz), 8.38~8.30 (1H, m), 7.90 (1H, d, J=2.0Hz), 7.88 (1H, d, J=8.8Hz), 7.77 (1H, d, J=7.8Hz), 7.55 (1H, d, J=2.3Hz), 7.46 (1H, d, J=2.0Hz), 7.28 (1H, dd, J=7.8, 4.9Hz), 7.07 (1H, dd, J=8.8, 2.3Hz), 3.87 (2H, s)	300<
259	1759, 1572, 1479, 1209, 1182, 1134	DMSO-d6: 9.24 (1H, s), 8.67~8.64 (1H, m), 8.40~8.37 (2H, m), 8.18 (1H, d, J=8.8Hz), 8.11 (1H, d, J=2.0Hz), 7.86 (1H, d, J=2.0Hz), 7.78 (1H, d, J=7.8Hz), 7.47 (1H, dd, J=8.8, 2.0Hz), 7.31~7.27 (1H, m), 3.92 (2H, s), 2.37 (3H, s), 2.36 (3H, s)	131.9-137.1
260	3028, 1579, 1489, 1219, 1034, 702	DMSO-d6: 8.98 (1H, s), 8.16 (1H, d, J=2.2Hz), 7.97 (1H, d, J=9.3Hz), 7.87 (1H, d, J=2.4Hz), 7.53 (1H, d, J=2.2Hz), 7.38 (2H, d, J=6.8Hz), 7.29~7.18 (4H, m), 3.94 (3H, s), 3.90 (3H, s), 3.89 (2H, s)	182.9-187.0

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
261	3300, 1558, 1450, 1392, 1319, 1200, 700	DMSO-d6: 10. 20～9. 41 (2H, m), 8. 92 (1H, s), 7. 89～7. 86 (2H, m), 7. 54 (1H, d, J=2. 4 Hz), 7. 44 (1H, d, J=2. 0Hz), 7. 38～7. 35 (2 H, m), 7. 28～7. 23 (2H, m), 7. 18～7. 12 (1H, m), 7. 03 (1H, dd, J=8. 8, 2. 4Hz), 3. 87 (2H, s)	350. 0<
262	3398, 1647, 1587, 1284, 1200, 1030, 818	DMSO-d6: 8. 82 (1H, d, J=7. 6Hz), 8. 14 (1H, d, J=2. 3Hz), 7. 98 (1H, d, J=8. 8Hz), 7. 84 (1H, d, J=2. 6Hz), 7. 51 (1H, d, J=2. 3Hz), 7. 18 (1H, dd, J=8. 8, 2. 6Hz), 6. 29 (1H, d, J= 7. 6Hz), 3. 96 (3H, s), 3. 90 (3H, s)	195. 0- 197. 2
263	3066, 1547, 1471, 1452, 1406, 1252	DMSO-d6: 10. 02 (1H, s), 9. 67 (1H, s), 8. 77 (1H, d, J=7. 4Hz), 7. 89 (1H, d, J=8. 6Hz), 7. 87 (1H, d, J=2. 0Hz), 7. 52 (1H, d, J=2. 3Hz), 7. 41 (1H, d, J=2. 0Hz), 7. 01 (1H, dd, J= 8. 6, 2. 3Hz), 6. 23 (1H, d, J=7. 4Hz)	300. 0<
264	3064, 1647, 1616, 1597, 1497, 1317, 814	DMSO-d6: 9. 01 (1H, d, J=7. 8Hz), 8. 72 (1H, d, J=1. 9Hz), 8. 48 (1H, d, J=2. 3Hz), 8. 20 (1H, d, J=8. 9Hz), 8. 07 (1H, d, J=1. 9Hz), 7. 74 (1H, dd, J=8. 9, 2. 3Hz), 6. 44 (1H, d, J= 7. 8Hz)	250. 0<
265	3051, 1643, 1610, 1500, 1321, 700	DMSO-d6: 9. 13 (1H, s), 8. 67 (1H, d, J=2. 0 Hz), 8. 45 (1H, d, J=2. 0Hz), 8. 14 (1H, d, J= 8. 7Hz), 8. 05 (1H, d, J=2. 0Hz), 7. 73 (1H, dd, J=8. 7, 2. 0Hz), 7. 38 (2H, d, J=7. 3Hz), 7. 26 (2H, dd, J=7. 3, 7. 3Hz), 7. 16 (1H, t, J= 7. 3Hz), 3. 88 (2H, s)	224. 9- 226. 6
266	3045, 1643, 1614, 1500, 1425, 1323, 802	DMSO-d6: 9. 19 (1H, s), 8. 67 (1H, d, J=2. 0 Hz), 8. 63 (1H, d, J=1. 7Hz), 8. 46 (1H, d, J= 2. 0Hz), 8. 39 (1H, dd, J=4. 8, 1. 7Hz), 8. 14 (1H, d, J=8. 9Hz), 8. 04 (1H, d, J=1. 7Hz), 7. 78～7. 73 (2H, m), 7. 29 (1H, dd, J=7. 9, 4. 8Hz), 3. 89 (2H, s)	255. 0- 257. 2
267	3053, 1647, 1603, 1500, 1323, 1221, 798	DMSO-d6: 9. 20 (1H, s), 8. 69 (1H, d, J=1. 8 Hz), 8. 47～8. 42 (3H, m), 8. 14 (1H, d, J=8. 8Hz), 8. 05 (1H, d, J=1. 8Hz), 7. 75 (1H, dd, J=8. 8, 2. 1Hz), 7. 36 (2H, d, J=5. 9Hz), 3. 89 (2H, s)	300. 0<

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
268	3053, 1643, 1608, 1497, 1321, 802	DMSO-d6: 9.07 (1H, s), 8.66 (1H, d, J=1.8 Hz), 8.45 (1H, d, J=2.0Hz), 8.14 (1H, d, J=8.6Hz), 8.04 (1H, d, J=1.8Hz), 7.73 (1H, dd, J=8.6, 2.0Hz), 7.29 (2H, d, J=8.6Hz), 6.82 (2H, d, J=8.6Hz), 3.80 (2H, s), 3.69 (3H, s)	199.9-202.1
269	3271, 1579, 1502, 1323, 1219, 806	DMSO-d6: 9.08 (1H, s), 8.71 (1H, d, J=1.8 Hz), 8.49 (1H, d, J=1.9Hz), 8.17 (1H, d, J=8.7Hz), 8.07 (1H, d, J=1.8Hz), 7.74 (1H, dd, J=8.7, 1.9Hz), 7.16 (2H, d, J=8.6Hz), 6.65 (2H, d, J=8.6Hz), 3.76 (2H, s)	300.0<
270	3323, 1676, 1608, 1500, 1323, 808	DMSO-d6: 9.84 (1H, s), 9.10 (1H, s), 8.69 (1H, d, J=1.3Hz), 8.47 (1H, d, J=1.7Hz), 8.16 (1H, d, J=8.6Hz), 8.06 (1H, d, J=1.3Hz), 7.74 (1H, dd, J=8.6, 1.7Hz), 7.45 (2H, d, J=9.2Hz), 7.28 (2H, d, J=9.2Hz), 3.82 (2H, s), 1.99 (3H, s)	300.0<
271	3462, 3346, 1624, 1500, 1321, 864	DMSO-d6: 8.95 (1H, s), 8.62 (1H, d, J=1.7 Hz), 8.41 (1H, d, J=2.1Hz), 8.10 (1H, d, J=8.7Hz), 8.01 (1H, d, J=1.7Hz), 7.70 (1H, dd, J=8.7, 2.1Hz), 7.02 (2H, d, J=8.4Hz), 6.47 (2H, d, J=8.4Hz), 4.85 (2H, bs), 3.69 (2H, s)	300.0<
272	3055, 1614, 1498, 1468, 1335, 1298, 1225	DMSO-d6: 9.35 (1H, d, J=2.2Hz), 9.30 (1H, s), 8.91 (1H, d, J=1.5Hz), 8.64~8.58 (2H, m), 8.40~8.39 (1H, m), 8.32 (1H, d, J=9.3Hz), 8.10 (1H, d, J=2.2Hz), 7.78 (1H, d, J=7.8Hz), 7.29 (1H, dd, J=7.8, 4.9Hz), 3.91 (2H, s)	311.3 (decomposition)
273	3336, 1637, 1579, 1558, 1508, 1489, 1311	DMSO-d6: 9.04 (1H, s), 8.62 (1H, s), 8.48 (1H, d, J=1.5Hz), 8.42~8.35 (1H, m), 7.97 (1H, d, J=1.5Hz), 7.78 (1H, d, J=8.6Hz), 7.75 (1H, d, J=7.3Hz), 7.36 (1H, d, J=2.1Hz), 7.28 (1H, dd, J=7.3, 4.9Hz), 6.90 (1H, dd, J=8.6, 2.1Hz), 5.42~5.36 (2H, m), 3.88 (2H, s)	307.1 (decomposition)
274	1593, 1560, 1475, 1321, 1265, 1215	DMSO-d6: 9.82 (1H, s), 9.11 (1H, s), 8.62~8.60 (2H, m), 8.42~8.36 (1H, m), 8.00 (1H, d, J=2.0Hz), 7.92 (1H, d, J=8.6Hz), 7.77~7.74 (1H, m), 7.65 (1H, d, J=2.1Hz), 7.28 (1H, dd, J=7.3, 4.9Hz), 7.11 (1H, dd, J=8.6, 2.1Hz), 3.88 (2H, s)	343.4 (decomposition)

Ex. No	IR (KBr, cm-1)	NMR (ppm) (*: 300MHz, unmarked 270MHz)	mp.(°C)
275	3307, 3082, 1647, 1585, 1495, 1309, 1190	DMSO-d6: 9. 81 (1H, s), 8. 91 (1H, d, J=7. 8 Hz), 8. 63 (1H, d, J=1. 8Hz), 8. 01 (1H, d, J=1. 8Hz), 7. 96 (1H, d, J=8. 8Hz), 7. 66 (1H, d, J=2. 4Hz), 7. 09 (1H, dd, J=8. 8, 2. 4Hz), 6. 37 (1H, d, J=7. 8Hz)	300. 0<
276	1647, 1605, 1576, 1502, 1329, 1275, 1236	DMSO-d6: 9. 12 (1H, s), 8. 63 (1H, s), 8. 49 (1H, d, J=2. 0Hz), 8. 39~8. 35 (2H, m), 8. 06~7. 93 (1H, m), 7. 81 (1H, d, J=2. 0Hz), 7. 78~7. 75 (2H, m), 7. 31~7. 29 (1H, m), 3. 89 (2H, s), 2. 60 (3H, s)	195. 8-196. 1
277	1643, 1601, 1502, 1323, 1273, 1242, 818	DMSO-d6: 8. 95 (1H, d, J=7. 8Hz), 8. 53 (1H, d, J=2. 0Hz), 8. 42~8. 40 (1H, m), 8. 11 (1H, d, J=8. 8Hz), 7. 99~7. 95 (1H, m), 7. 83~7. 75 (1H, m), 6. 39 (1H, d, J=7. 8Hz), 2. 62 (3H, s)	255. 7-258. 9

Table 6



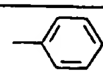
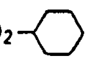
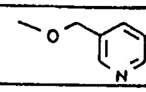
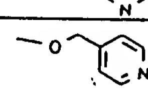
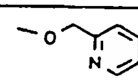
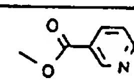
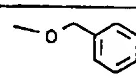
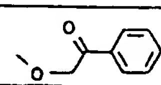
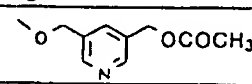
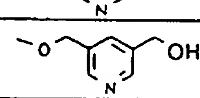
Ex. No.	R^1
1	$-OCH_3$
2	$-OH$
3	$-OCH_2CO_2C(CH_3)_3$
4	$-OCH_2CO_2CH(CH_3)_2$
5	$-OCH_2CO_2CH_2CH_3$
6	$-OCH_2CO_2H$
7	$-OCH_2CO_2CH_2CH_2CH_3$
8	$-OC(CH_3)_2CO_2CH_2CH_3$
9	$-OC(CH_3)_2CO_2H$
10	$-OCH_2CH_2CH_2CO_2CH_2CH_3$
11	$-OCH_2CH_2CH_2CO_2H$
12	$-OCH_2CO_2CH_2$ 
13	$-OCH_2CO_2CH_3$
14	$-OCH_2CO_2(CH_2)_4CH_3$
15	$-OCH_2CO_2$ 
16	$-OCH_2CO_2(CH_2)_2N(CH_3)_2$
17	$-OCH=CHCH_2CO_2H$
18	
19	
20	
21	
22	
23	
24	
25	
26	$-OCH_2CH_2CH_2OH$
27	$-OCH_2CH_2CH_2CH_2OH$
28	$-OCH_2CH_2CH_2CH_2CH_2OH$
29	$-OCH_2(CH_2)_4CH_2OH$
30	$-OCH_2CH_2OCH_2CH_2OH$

Table 6 (contd.)

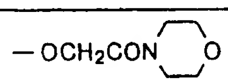
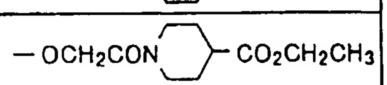
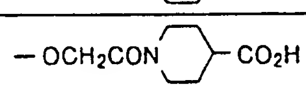
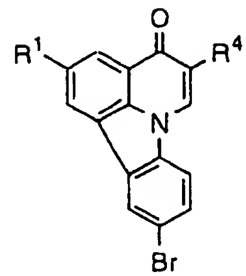
Ex. No.	R^1
31	$-OCH_2C(CH_3)_2CH_2OH$
32	$-OCH_2COCH_2CH_2OH$
33	$-OCH_2CH_3$
34	$-OCH_2CH_2CH_2CH_3$
35	$-OCH_2CH_2OCH_3$
36	$-OCH_2CH_2OCH_2CH_3$
37	$-OCH_2CH(OCH_2CH_3)_2$
38	$-OCOCH_3$
39	$-OCH_2COCH_2CH_3$
40	$-OCH_2COCH_2CH_2CH_3$
41	$-OCH_2CH(OH)CH_2CH_2CH_3$
42	$-OCH_2COC(CH_3)_3$
43	$-OCH_2CONHCH_2CH_3$
44	
45	
46	
47	$-OCH_2CONHCH_2OH$

Table 7



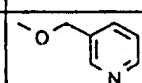
Ex. No.	R^1	R^4
48	$-OCH_3$	$-CH_3$
49	$-OH$	$-CH_3$
50	$-OCH_2CO_2C(CH_3)_3$	$-CH_3$
51	$-OCH_2CO_2CH(CH_3)_2$	$-CH_3$
52	$-OCH_2CO_2CH_2CH_3$	$-CH_3$
53	$-OCH_2CO_2H$	$-CH_3$
54		$-CH_3$
55	$-OCH_2(CH_2)_2CH_2OH$	$-CH_3$
56	$-OCOCH_3$	$-CH_3$
57	$-OCH_2CO(CH_2)_2CH_3$	$-CH_3$
58	$-OCH_3$	$-H$
59	$-OH$	$-H$
60	$-OCH_2CO_2C(CH_3)_3$	$-H$

Table 7 contd.

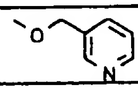
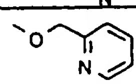
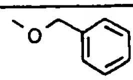
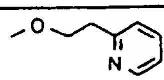
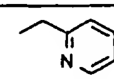
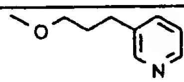
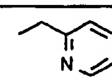
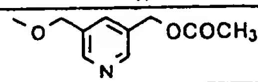
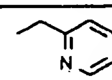
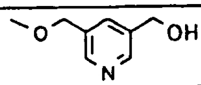
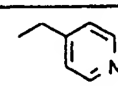
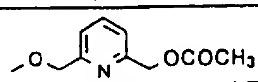
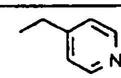
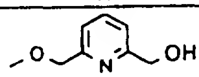
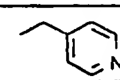
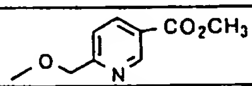
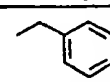
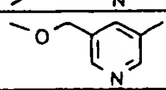
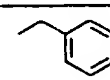
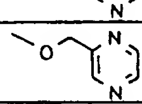
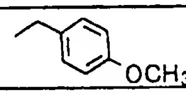
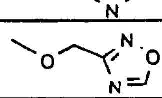
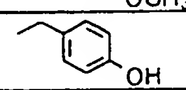
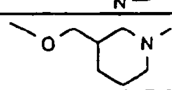
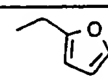
Ex. No.	R^1	R^4	Ex. No.	R^1	R^4
61	$-OCH_2CO_2CH(CH_3)_2$	$-H$	78	$-O(CH_2)_3N(CH_3)_2$	$-H$
62	$-OCH_2CO_2CH_2CH_3$	$-H$	79	$-O(CH_2)_3CH_2OH$	$-H$
63	$-OCH_2CO_2H$	$-H$	80	$-O(CH_2)_4CH_2OH$	$-H$
64		$-H$	81	$-O(CH_2)_5CH_2OH$	$-H$
65		$-H$	82	$-OCOCH_3$	$-H$
66		$-H$	83	$-OCH_2CO(CH_2)_2CH_3$	$-H$
67		$-H$	84	$-OCH_3$	
68		$-H$	85	$-OH$	
69		$-H$	86	$-OCH_2CO_2C(CH_3)_3$	
70		$-H$	87	$-OCH_3$	
71		$-H$	88	$-OH$	
72		$-H$	89	$-OCH_2CO_2C(CH_3)_3$	
73		$-H$	90	$-OCH_3$	
74		$-H$	91	$-OH$	
75		$-H$	92	$-OCH_3$	
76		$-H$	93	$-OH$	
77		$-H$	94	$-OCH_3$	

Table 7 contd.

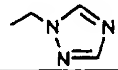
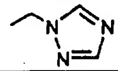
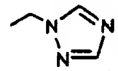
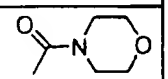
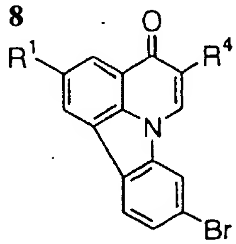
Ex. No.	R^1	R^4
95	$-OCH_3$	
96	$-OH$	
97	$-OCOCH_3$	
98	$-OCH_3$	$-CO_2CH_2CH_3$
99	$-OCH_3$	$-CO_2H$
100	$-OCH_3$	

Table 8



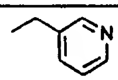
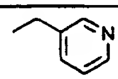
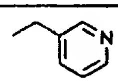
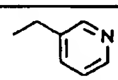
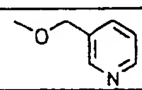
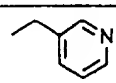
Ex. No.	R^1	R^4
101	$-OCH_3$	
102	$-OH$	
103	$-OCH_2CO_2C(CH_3)_3$	
104	$-OCH_2CO_2H$	
105		

Table 8 contd.

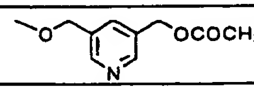
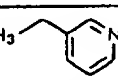
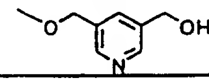
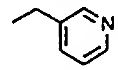
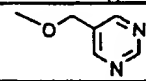
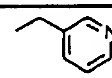
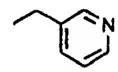
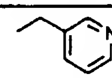
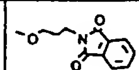
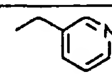
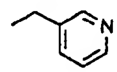
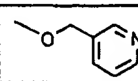
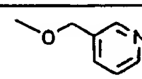
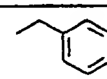
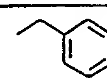
Ex. No.	R^1	R^4
106		
107		
108		
109	$-OCH_2CONHCH_2CH_3$	
110	$-O(CH_2)_2CH_2OH$	
111		
112	$-O(CH_2)_2CH_2NH_2$	
113	$-OCH_3$	$-CH_3$
114	$-OH$	$-CH_3$
115		$-CH_3$
116	$-OCH_3$	$-H$
117	$-OH$	$-H$
118	$-OCH_2CO_2C(CH_3)_3$	$-H$
119	$-OCH_2CO_2H$	$-H$
120		$-H$
121	$-OCH_3$	
122	$-OH$	

Table 8 contd.

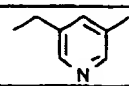
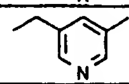
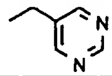
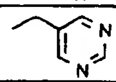
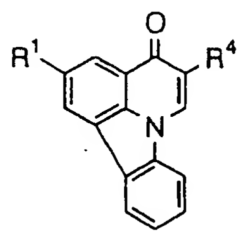
Ex. No.	R^1	R^4
123	$-OCH_3$	
124	$-OH$	
125	$-OCH_3$	
126	$-OH$	

Table 9



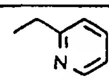
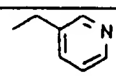
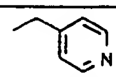
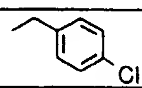
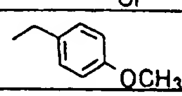
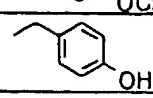
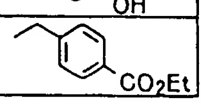
Ex. No.	R^1	R^4
127	$-H$	
128	$-H$	
129	$-H$	
130	$-H$	
131	$-H$	
132	$-H$	
133	$-H$	

Table 9 contd.

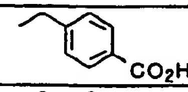
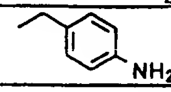
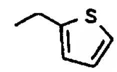
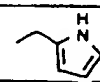
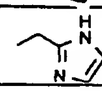
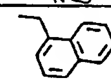
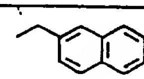
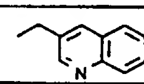
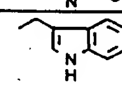
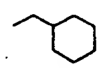
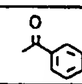
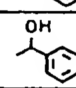
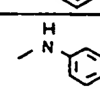
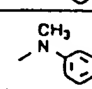
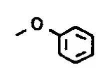
Ex. No.	R^1	R^4
134	$-H$	
135	$-H$	
136	$-H$	
137	$-H$	
138	$-H$	
139	$-H$	
140	$-H$	
141	$-H$	
142	$-H$	
143	$-H$	
144	$-H$	
145	$-H$	
146	$-H$	
147	$-H$	
148	$-H$	
149	$-H$	
150	$-H$	$-Br$

Table 9 contd.

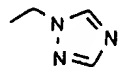
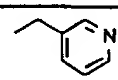
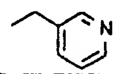
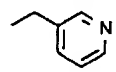
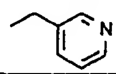
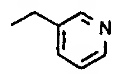
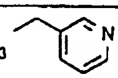
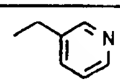
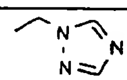
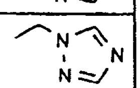
Ex. No.	R^1	R^4
151	$-H$	$-CH(OH)CH_2CH_3$
152	$-H$	$-CH_3$
153	$-H$	
154	$-OCH_3$	
155	$-OH$	
156	$-OCOCH_3$	
157	$-OCH_2CO_2CH_2CH_3$	
158	$-OCH_2CO_2H$	
159	$-O(CH_2)_3CO_2CH_2CH_3$	
160	$-O(CH_2)_2CH_2CO_2H$	
161	$-OCH_3$	$-CH_3$
162	$-OH$	$-CH_3$
163	$-OCOCH_3$	$-CH_3$
164	$-OCH_2CO_2CH_2CH_3$	$-CH_3$
165	$-OCH_2CO_2H$	$-CH_3$
166	$-OCH_3$	
167	$-OH$	

Table 9 contd.

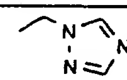
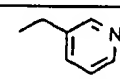
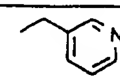
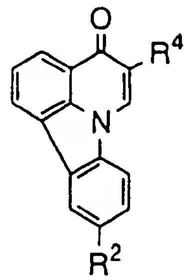
Ex. No.	R^1	R^4
168	$-OCOCH_3$	
169	$-OCH_3$	$-H$
170	$-OH$	$-H$
171	$-Cl$	$-H$
172	$-Cl$	$-CH_3$
173	$-CN$	$-H$
174	$-CONH_2$	$-H$
175	$-CO_2H$	$-H$
176	$-CO_2CH_3$	$-H$
177	$-CH_2OH$	$-H$
178	$-Br$	
179	$-NH_2$	
180	$-Br$	$-H$
181	$-NH_2$	$-H$
182	$-NHCH_2CH_2CH_3$	$-H$
183	$-NHCOCH_3$	$-H$

Table 10



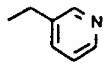
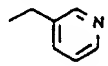
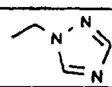
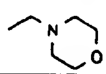
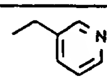
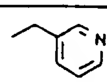
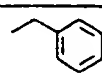
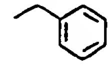
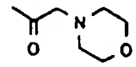
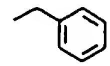
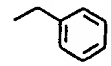
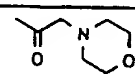
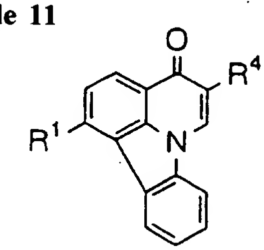
Ex. No.	R^2	R^4
184	$-Br$	
185	$-OCH_3$	
186	$-OH$	
187	$-Br$	$-H$
188	$-OCH_3$	$-H$
189	$-OH$	$-H$
190	$-Cl$	$-CH_3$
191	$-Cl$	
192	$-Cl$	
193	$-Cl$	$-H$
194	$-COCH_3$	
195	$-CO_2H$	
196	$-COCH_3$	
197	$-CO_2H$	
198		
199	$-CH(OH)CH_3$	
200	$-COCH_3$	$-H$
201	$-CO_2H$	$-H$
202		$-H$

Table 11



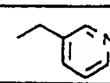
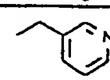
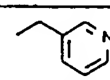
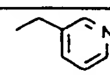
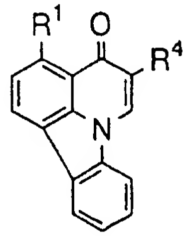
Ex. No.	R^1	R^4
203	$-OCH_3$	
204	$-OH$	
205	$-OCOCH_3$	
206	$-OCH_2CO_2CH_2CH_3$	
207	$-OCH_3$	$-H$

Table 11 contd.

Ex. No.	R^1	R^4
208	$-OH$	$-H$
209	$-OCOCH_3$	$-H$

Table 12



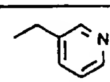
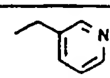
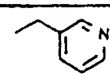
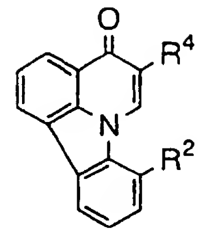
Ex. No.	R^1	R^4
210	$-OCH_3$	
211	$-OH$	
212	$-OCOCH_3$	
213	$-OCH_3$	$-H$
214	$-OH$	$-H$
215	$-OCOCH_3$	$-H$

Table 13



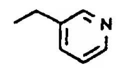
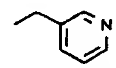
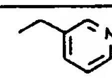
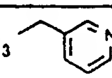
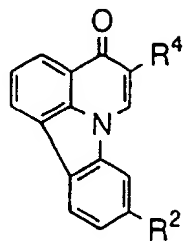
Ex. No.	R^2	R^4
216	$-OCH_3$	
217	$-OH$	
218	$-OCOCH_3$	
219	$-OCH_2CO_2CH_2CH_3$	
220	$-OCH_3$	$-H$
221	$-OH$	$-H$
222	$-OCOCH_3$	$-H$
223	$-OCH_2CO_2CH_2CH_3$	$-H$

Table 14



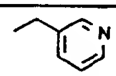
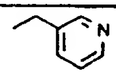
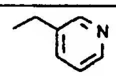
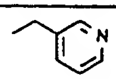
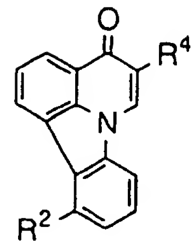
Ex. No.	R^2	R^4
224	$-OCH_3$	
225	$-OH$	
226	$-OCOCH_3$	
227	$-OCH_2CO_2CH_2CH_3$	
228	$-OCH_3$	$-H$
229	$-OH$	$-H$
230	$-OCOCH_3$	$-H$
231	$-OCH_2CO_2CH_2CH_3$	$-H$

Table 15



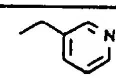
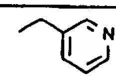
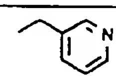
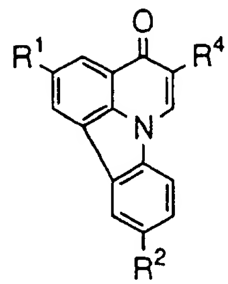
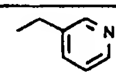
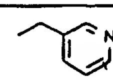
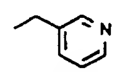
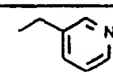
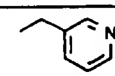
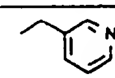
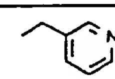
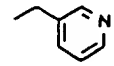
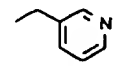
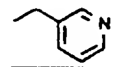
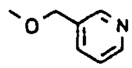
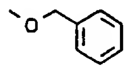
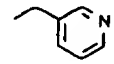
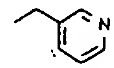
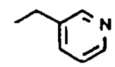
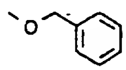
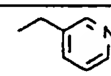
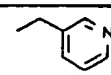
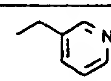
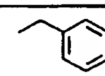
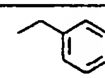
Ex. No.	R^2	R^4
232	$-OCH_3$	
233	$-OH$	
234	$-OCOCH_3$	

Table 16



Ex. No.	R^1	R^2	R^4
235	$-OCH_3$	$-F$	
236	$-OH$	$-F$	
237	$-OCOCH_3$	$-F$	
238	$-OCOCH_2CH_2CH_3$	$-F$	
239	$-OCH_3$	$-F$	$-H$
240	$-OH$	$-F$	$-H$
241	$-OCOCH_3$	$-F$	$-H$
242	$-OCOCH_2CH_2CH_3$	$-F$	$-H$
243	$-OCH_3$	$-Cl$	
244	$-OH$	$-Cl$	
245	$-OCH_2CO_2CH_2CH_3$	$-Cl$	
246	$-OCH_3$	$-Cl$	$-H$
247	$-OH$	$-Cl$	$-H$

Ex. No.	R^1	R^2	R^4
248	$-OCH_3$	$-CH_2CH_3$	
249	$-OH$	$-CH_2CH_3$	
250	$-OCH_2CO_2CH_2CH_3$	$-CH_2CH_3$	
251		$-CH_2CH_3$	
252		$-OCH_3$	
253	$-OH$	$-OCH_3$	
254	$-OCH_2CO_2CH_2CH_3$	$-OCH_3$	
255		$-OCH_3$	$-H$
256	$-OH$	$-OCH_3$	$-H$
257	$-OCH_3$	$-OCH_3$	
258	$-OH$	$-OH$	
259	$-OCOCH_3$	$-OCOCH_3$	
260	$-OCH_3$	$-OCH_3$	
261	$-OH$	$-OH$	
262	$-OCH_3$	$-OCH_3$	$-H$
263	$-OH$	$-OH$	$-H$
264	$-Cl$	$-Cl$	$-H$

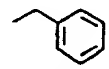
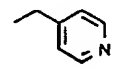
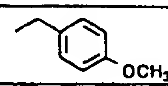
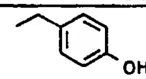
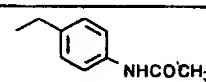
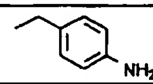
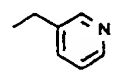
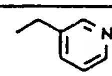
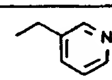
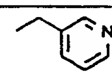
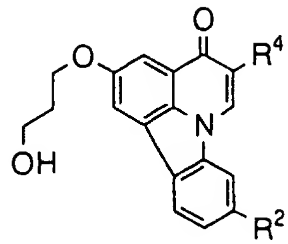
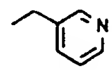
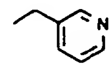
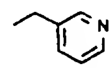
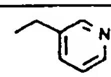
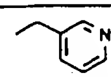
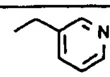
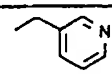
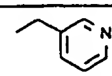
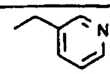
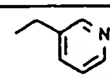
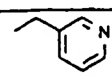
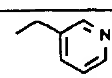
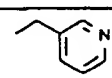
Ex. No.	R^1	R^2	R^4
265	$-Cl$	$-Cl$	
266	$-Cl$	$-Cl$	
267	$-Cl$	$-Cl$	
268	$-Cl$	$-Cl$	
269	$-Cl$	$-Cl$	
270	$-Cl$	$-Cl$	
271	$-Cl$	$-Cl$	
272	$-Cl$	$-NO_2$	
273	$-Cl$	$-NH_2$	
274	$-Cl$	$-OH$	
275	$-Cl$	$-OH$	$-H$
276	$-CH_3$	$-Br$	
277	$-CH_3$	$-Br$	$-H$

Table 17



Ex. No.	R^2	R^4
279	—Br	 $\cdot CH_3SO_3H$
280	—Br	 $\cdot HNO_3$
281	—Br	 $\cdot H_2SO_4$
282	—Br	 $\cdot HO_2CCH{=}CHCO_2H$
283	—Cl	
284	—Cl	 $\cdot HCl$
285	—Cl	 $\cdot CH_3SO_3H$
286	—F	
287	—F	 $\cdot CH_3SO_3H$
288	—H	
289	$-CF_3$	
290	$-CF_3$	 $\cdot HCl$
291	$-CF_3$	 $\cdot CH_3SO_3H$

Preparation Example 1

Tablets

Compound of Example 3	100 g
Lactose	350 g
Potato starch	120 g
Polyvinyl alcohol	15 g
Magnesium stearate	15 g

The aforesaid components were weighed out and thereafter the compound of Example 3, lactose and potato starch were uniformly mixed. An aqueous solution of polyvinyl alcohol was added to this mixture and granules were prepared using a wet type granule granulation method. These granules were dried, magnesium stearate was admixed, and thereafter, tablets 300 mg in weight were formed by pressurised tabletting.

Preparation Example 2

Encapsulated formulation

Compound of Example 50	50 g
Lactose	435 g
Magnesium stearate	15 g

The aforesaid components were weighed and thereafter mixed uniformly. The mixture was filled in an amount of 300 mg by weight into suitable hard capsules using a capsule inclusion device, and an encapsulated formulation was formed.

Preparation Example 3

Injection

Compound of Example 105	2 g
Propylene glycol	200 g
Distilled water for injection	suitable quantity

The aforesaid components were weighed and thereafter the compound of Example 105 was dissolved in propylene glycol. The total quantity was made up to 1,000 ml by the addition of sterile water for injection, and after sterilising by filtration, this solution was introduced in an amount of 5 ml into 10

ml ampules and the ampules heat-sealed, and injection preparations thereby made.

Preparation Example 4

Suppository

Compound of Example 110	100 g
Polyethylene glycol 1500	180 g
Polyethylene glycol 4000	720 g

The compound of Example 110 was thoroughly pulverized in a mortar and formed into a fine powder, and thereafter 1 g suppositories were formed by a fusion method.

Preparation Example 5

Powder

Compound of Example 51	200 g
Lactose	790 g
Magnesium stearate	10 g

The aforesaid components were respectively weighed and thereafter mixed uniformly and a 20 % powder was made.

Possible Applications in Industry

The compounds having a pyridocarbazole skeleton of this invention have extremely high PDE type V enzyme inhibition selectivity. Moreover, the compounds of this invention show effectiveness in animal model tests, and moreover have extremely low toxicity and little side effects, and therefore the said compounds are useful as drugs in the clinical field and in animals, and in particular they are expected to demonstrate an increased preventive and/or therapeutic effect on pulmonary hypertension, ischemic cardiac diseases and diseases in which a cGMP-PDE inhibitory action is effective.

Moreover, the medicinal compositions of this invention are effective in the prevention or therapy of pulmonary hypertension, ischemic cardiac disease and diseases in which cGMP-PDE inhibitory action is effective. Pulmonary hypertension is a general term for various diseases presenting pulmonary hypertension, and examples of such diseases include chronic bronchitis, periphery respiratory tract lesion, lung emphysema, bronchiectasis, sarcoidosis, tuberculosis after-effect, diffuse

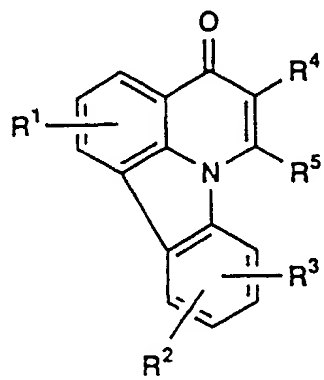
interstitial pneumonia, diffuse bronchiolitis, asthma, pulmonary fibrosis, collagen disease, pulmonary thromboembolism, pulmonary veno-occlusion, lung vasculitis, primary pulmonary hypertension and the like, and whereby progressed states thereof such as in the case of pulmonary heart are also included. Patients presenting pulmonary hypertension have a disturbance in pulmonary circulation due to pulmonary vascular occlusion, and develop cyanosis and dyspnea. Palpitation, pectoralgia are often caused and coughing is also often seen. The medicinal compositions of this invention are effective for such aforesaid various symptoms. Moreover, ischemic heart disease is a general term for diseases generated due to circulatory disorders in the heart as a result of various causes, and angina of effort, rest angina, unstable angina, variant angina, acute cardiac insufficiency, chronic heart failure, cardiac infarction, heart edema, arrhythmia or the like may be proposed. Moreover, the medicinal compositions of this invention markedly increase cGMP, and therefore can be used in arterial sclerosis, restenosis after PTCA or the like, thrombosis (thrombosis occurred due to injury of blood vessel wall, arteriosclerosis, vasculitis, platelet aggregation or the like) or the like. Moreover, as diseases in which cGMP-PDE inhibitory action is effective, in addition to the aforesaid diseases, the said compositions can be used for diseases in which an increase in cGMP would be considered to be effective, such as asthma, chronic obstructive lung disease (bronchitis, lung emphysema), glomerular disease including glomerulonephritis and diabetic nephropathy, renal failure, nephritis edema, disease of urinary organ and generative organ (for example prostate gland hypertrophy, erectile dysfunction and incontinence), peripheral circulation disorder, peripheral vascular disease, cerebral circulation disorder (cerebral infarction or the like), cerebral function disorder, dementia, allergic disease (atopic dermatitis, allergic rhinitis), hypertension and the like. In particular, they are usable for glomerular diseases including glomerulonephritis and diabetic nephropathy, renal failure, nephritis edema and diseases of the urinary organs and generative organs (for example prostate gland hypertrophy, erectile dysfunction and incontinence). Renal failure is a pathological state or clinical various symptoms due to a lowering of the renal function as a result of various causes, namely a fall in the quantity of glomerular filtration (GFR). Moreover, some glomerular bodies show a sclerotic image in chronic renal failure, and the renal failure is thought to progress with the spread of sclerosis to glomerular bodies with less disorder. As a result, the accumulation in the body of various excretion substances proceeds and so-called uremia occurs. Moreover, polyurea and night time urination are also observed due to condensation ability disorder. During the renal failure, when an unsuitable Na or water load is present, adequate compensation is not possible due to the decreased GFR, and edema, lung edema, congestive heart failure, hypertension or the like are observed. The medicinal compositions of this invention are effective against such aforesaid various symptoms.

Using the process for the production of this invention, compounds having a pyridocarbazole skeleton that have a PDE type V inhibitory action with extremely high enzyme inhibition selectivity can be produced.

Translator's note (as per page 2 of this translation): In many of the sections of this patent application where production processes are outlined, the Japanese grammar used and lack of formula and reaction equation including formula, make it impossible to determine what is meant. It is almost as if the application is being deliberately obtuse. Readers of this translation should bear this in mind in particular on pages 12 to 14 and 37 to 38, and also at Claim 6.

Patent Claims

1. A compound represented by following formula (I) or a salt thereof.



(I)

(in the formula, R^1 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, alkoxycarbonyl group of carbon number 1-4, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, 2-hydroxypentyloxy group, 2,2-diethoxyethoxy group, optionally protected hydroxy group, optionally protected mercapto group, straight chain or branched chain alkanoyloxy group of carbon number 1-4, carbonyloxy group substituted by a phenyl group or pyridyl group, straight chain or branched chain alkyl group of carbon number 1-4 optionally substituted by one hydroxy group, an amino group optionally mono- or di-substituted by an alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3 optionally mono-substituted by a group arbitrarily selected from hydroxy group • carboxyl group • phenyl group or pyridyl group, or following formula (XXI)

$-O-(CH_2)_n-Z$ (XXI)

(in the formula, Z denotes a hydrogen atom, carboxyl group, alkoxy group of carbon number 1 or 2 optionally substituted by one hydroxy group, alkoxycarbonyl group of carbon number 1-6, a carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or alkyl group of carbon number 1 or 2, alkanoyl group of carbon number 1-4 optionally substituted by one hydroxy group or mercapto group, piperidinylcarbonyl group optionally substituted by one carboxyl group or alkoxy carbonyl group of carbon number 1 or 2, morpholylcarbonyl group, hydroxy group, mercapto

group, amino group, phenyl group, pyridyl group optionally mono-substituted by a hydroxymethyl group • acetoxymethyl group • alkyl group of carbon number 1-4 or alkoxycarbonyl group of carbon number 1 or 2, pyrazinyl group, pyrimidinyl group, furyl group, thienyl group, oxadiazolyl group, 4-methoxyphenoxy group, and n denotes 1 to 6);

R^2 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, 4-morpholylacetyl group, straight chain or branched chain alkanoyloxy group of carbon number 1-4, straight chain or branched chain alkanoyl group of carbon number 1-4, straight chain or branched chain alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3 optionally mono-substituted by a group arbitrarily selected from hydroxy group • carboxyl group • phenyl group or pyridyl group, or straight chain or branched chain alkoxy group of carbon number 1-4 optionally substituted by one alkoxycarbonyl group of carbon number 1-4;

R^3 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group or a straight chain or branched chain alkoxy group of carbon number 1-4;

R^4 denotes a hydrogen atom, halogen atom, optionally protected carboxyl group, phenoxy group, anilino group, N-methylanilino group, 4-morpholylcarbonyl group, alkyl group of carbon number 1 or 2 optionally substituted by a cyclic alkyl group of carbon number 3-6, a benzyl group optionally mono- or di-substituted at phenyl moiety with a group arbitrarily selected from halogen atom • hydroxy group • mercapto group • alkoxy group of carbon number 1 or 2 • alkylthio group of carbon number 1 or 2 • alkoxycarbonyl group of carbon number 1-4 • acetylamino group • carboxyl group or amino group, pyridylmethyl group optionally substituted by an alkyl group of carbon number 1-4, morpholyl methyl group, triazolylmethyl group, furylmethyl group, thienylmethyl group, pyrimidinylmethyl group, pyrazinylmethyl group, pyrrolylmethyl group, imidazolylmethyl group, quinolylmethyl group, indolylmethyl group, naphthylmethyl group, benzoyl group, α-hydroxybenzyl group, or an alkoxycarbonyl group of carbon number 1 or 2;

R^5 denotes a hydrogen atom or methyl group;

when R^1, R^2, R^3 and R^5 are simultaneously hydrogen atoms, R^4 is not hydrogen atom, benzyl group, 4-diethylaminobenzyl group or furylmethyl group).

2. A compound or a salt thereof in accordance with Claim 1, wherein the substitution position of aforesaid R^1 is 2-position, and the substitution position of R^2 is 9- or 10-position, R^2 is a hydrogen atom, halogen atom, hydroxy group, trifluoromethyl group or a straight chain or branched chain alkoxy group of carbon number 1-4, and R^3 is a hydrogen atom.

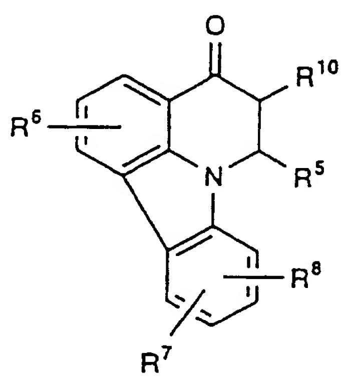
3. A compound or a salt thereof in accordance with Claim 1 or 2, wherein aforesaid R^4 is a hydrogen atom, alkyl group of carbon number 1 or 2, pyrimidinylmethyl group, pyridylmethyl group optionally substituted by a methyl group.

4. A compound or a salt thereof in accordance with Claims 1-3, wherein the substitution position of aforesaid R^1 is 2-position, and R^1 is a hydroxy group, or following formula (XXI)

$-O-(CH_2)_n-Z$ (XXI)

(in the formula, Z denotes a hydrogen atom, carboxyl group, a carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or alkyl group of carbon number 1 or 2, alkanoyl group of carbon number 1-4 optionally substituted by one hydroxy group or mercapto group, hydroxy group, phenyl group, pyridyl group, pyrazinyl group, pyrimidinyl group, and n denotes 1 to 4); R^2 is a halogen atom or trifluoromethyl group in the substitution position 9; R^3 is a hydrogen atom; R^4 is a methyl group, pyrimidinylmethyl group or pyridylmethyl group; and R^5 is a hydrogen atom.

5. A compound represented by following formula (IV) or a salt thereof, useful for the synthesis of the aforesaid compound of formula (I) or a salt thereof.

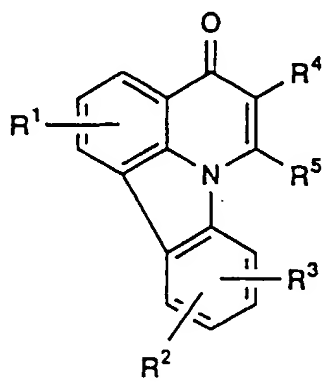


(IV)

(in the formula, R^5 is a hydrogen atom or methyl group, R^6 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, alkoxycarbonyl group of carbon number 1-4, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, optionally protected hydroxy group, optionally protected mercapto group, straight chain or branched chain alkyl group of carbon number 1-4 optionally substituted by one hydroxy group, an amino group optionally mono- or di-substituted by an alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3, or straight chain alkoxy group of carbon number 1-6 optionally substituted by a 4-methoxyphenoxy group; R^7 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, straight chain or branched chain alkanoyl group of carbon number 1-4, straight chain or branched chain alkyl group of carbon number 1-4, straight chain or branched chain

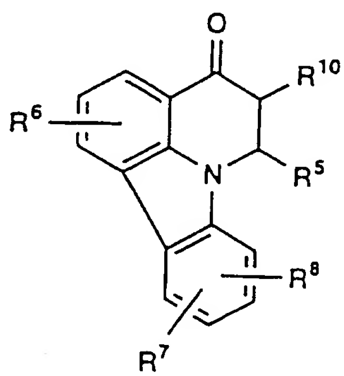
alkoxy group of carbon number 1-4; R^8 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, or straight chain or branched chain alkoxy group of carbon number 1-4; R^{10} denotes a hydrogen atom, halogen atom, phenoxy group, an α-hydroxybenzyl group, anilino group, N-methylanilino group, methyl group, or halomethyl group).

6. A process for the production of a compound of the following formula (I) or a salt thereof



(I)

(in the formula, R^1, R^2, R^3 and R^4 have the same aforesaid meanings, and R^5 denotes a hydrogen atom or a methyl group)
wherein a compound of the following formula (IV)



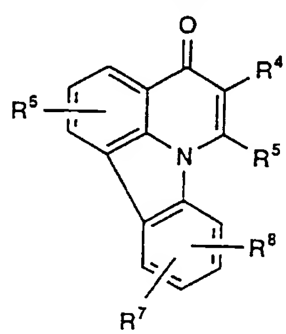
(IV)

(in the formula, R^5 has the same aforesaid meaning, R^6 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, alkoxycarbonyl group of carbon number 1-4, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, optionally protected hydroxy group, optionally protected mercapto group, straight chain or branched chain alkyl group of carbon number 1-4 optionally substituted by one hydroxy group, an amino group optionally mono- or di-substituted by an alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3, or straight chain alkoxy group of carbon number 1-6 optionally substituted by a 4-methoxyphenoxy group; R^7 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally

protected carboxyl group, straight chain or branched chain alkanoyl group of carbon number 1-4, straight chain or branched chain alkyl group of carbon number 1-4, or straight chain or branched chain alkoxy group of carbon number 1-4; R^8 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, or straight chain or branched chain alkoxy group of carbon number 1-4; and R^{10} denotes a hydrogen atom, halogen atom, phenoxy group, an α-hydroxybenzyl group, anilino group, N-methylanilino group, methyl group, or halomethyl group)
or a salt thereof, if necessary, under basic conditions, is reacted with an aldehyde derivative of the following formula (XIX)

R^{12}-CHO (XIX)

(in the formula, R^{12} denotes a hydrogen atom, methyl group, a cyclic alkyl group of carbon number 3-6, a phenyl group optionally mono- or di-substituted by a group arbitrarily selected from halogen atom, • hydroxy group • mercapto group • alkoxy group of carbon number 1 or 2 • alkylthio group of carbon number 1 or 2 • alkoxycarbonyl group of carbon number 1-4 • acetylamino group • carboxyl group or amino group, a pyridyl group optionally substituted by an alkyl group of carbon number 1-4, morpholyl group, triazolyl group, furyl group, thienyl group, pyrimidinyl group, pyrazinyl group, pyrrolyl group, imidazolyl group, quinolyl group, indolyl group, or naphthyl group)
then, an oxidation reaction is performed either on the compound as it is or the compound wherein the double bond of the enone formed by dehydration is isomerized in the ring; or reacting with for example phenol, aniline, N-methylaniline, triazole, imidazole, morpholine and the like, and then performing the oxidation reaction;
or the compound represented by the following formula (XXII)



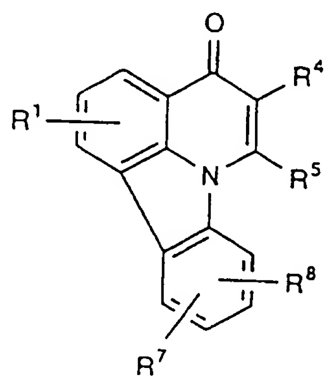
(XXII)

(in the formula, R^4, R^5, R^6, R^7 and R^8 have the same aforesaid meanings) obtained by the oxidation reaction is derivatized, or a suitable substitution reaction is performed, or the protecting group is removed if necessary from R^6, and the compound is reacted with a reactive halogen derivative represented by the following formula (XX)

R^{13}-X (XX)

(in the formula, X denotes a halogen atom; R^{13} denotes an alkoxycarbonyl group of carbon number 1-4, 3-carboxy-1-propenyl group, 2,2-diethoxyethyl group, straight chain or branched chain

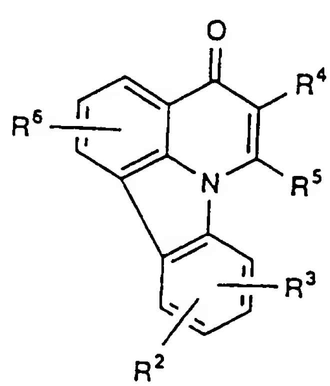
alkanoyl group of carbon number 1-4, a carbonyl group which is substituted by a phenyl group or pyridyl group, or the group -$(CH_2)_n$-Z (Z denotes a hydrogen atom, carboxyl group, alkoxy group of carbon number 1 or 2 optionally substituted by one hydroxy group, alkoxycarbonyl group of carbon number 1-6, a carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or alkyl group of carbon number 1 or 2, alkanoyl group of carbon number 1-4 optionally substituted by one hydroxy group or mercapto group, piperidinylcarbonyl group optionally substituted by one carboxyl group or alkoxy carbonyl group of carbon number 1 or 2, morpholylcarbonyl group, hydroxy group, mercapto group, amino group, phenyl group, pyridyl group optionally mono-substituted by a hydroxymethyl group • acetoxymethyl group • alkyl group of carbon number 1-4 or alkoxycarbonyl group of carbon number 1 or 2, pyrazinyl group, pyrimidinyl group, furyl group, thienyl group, oxadiazolyl group, 4-methoxyphenoxy group, and n denotes 1 to 6); to obtain a compound represented by the following formula (XXIII)



(XXIII)

(in the formula, R^1, R^4, R^5, R^7 and R^8 have the same aforesaid meanings) and performing a suitable substitution reaction;

or the compound represented by the following formula (XXIV)

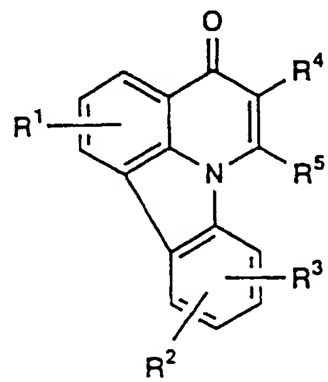


(XXIV)

(in the formula, R^2, R^3, R^4, R^5 and R^6 have the same aforesaid meanings) is obtained from the compound represented by the aforesaid formula (XXII) by performing a suitable substitution reaction,

and if necessary, removing the protecting group from R^6, and reacting with the aforesaid reactive halogen derivative of formula (XX).

7. A preventive or therapeutic agent of pulmonary hypertension containing a compound represented by following formula (I) or a salt thereof as an effective component.



(I)

(in the formula, R^1 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, alkoxycarbonyl group of carbon number 1-4, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, 2-hydroxypentyloxy group, 2,2-diethoxyethoxy group, optionally protected hydroxy group, optionally protected mercapto group, straight chain or branched chain alkanoyloxy group of carbon number 1-4, carbonyloxy group substituted by a phenyl group or pyridyl group, straight chain or branched chain alkyl group of carbon number 1-4 optionally substituted by one hydroxy group, an amino group optionally mono- or di-substituted by an alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3 optionally mono-substituted by a group arbitrarily selected from hydroxy group • carboxyl group • phenyl group or pyridyl group, or following formula (XXI)

$-O-(CH_2)_n-Z$ (XXI)

(in the formula, Z denotes a hydrogen atom, carboxyl group, alkoxy group of carbon number 1 or 2 optionally substituted by one hydroxy group, alkoxycarbonyl group of carbon number 1-6, a carbamoyl group optionally mono- or di-substituted by a hydroxymethyl group or alkyl group of carbon number 1 or 2, alkanoyl group of carbon number 1-4 optionally substituted by one hydroxy group or mercapto group, piperidinylcarbonyl group optionally substituted by one carboxyl group or alkoxy carbonyl group of carbon number 1 or 2, morpholinocarbonyl group, hydroxy group, mercapto group, amino group, phenyl group, pyridyl group optionally mono-substituted by a hydroxymethyl group • acetoxymethyl group • alkyl group of carbon number 1-4 or alkoxycarbonyl group of carbon number 1 or 2, pyrazinyl group, pyrimidinyl group, furyl group, thienyl group,

oxadiazolyl group, 4-methoxyphenoxy group, and n denotes 1 to 6);

R^2 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, 4-morpholylacetyl group, straight chain or branched chain alkanoyloxy group of carbon number 1-4, straight chain or branched chain alkanoyl group of carbon number 1-4, straight chain or branched chain alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3 optionally mono-substituted by a group arbitrarily selected from hydroxy group • carboxyl group • phenyl group or pyridyl group, or straight chain or branched chain alkoxy group of carbon number 1-4 optionally substituted by one alkoxycarbonyl group of carbon number 1-4;

R^3 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group or a straight chain or branched chain alkoxy group of carbon number 1-4;

R^4 denotes a hydrogen atom, halogen atom, optionally protected carboxyl group, phenoxy group, anilino group, N-methylanilino group, 4-morpholylcarbonyl group, alkyl group of carbon number 1 or 2 optionally substituted by a cyclic alkyl group of carbon number 3-6, a benzyl group optionally mono- or di-substituted at phenyl moiety with a group arbitrarily selected from halogen atom, • hydroxy group • mercapto group • alkoxy group of carbon number 1 or 2 • alkylthio group of carbon number 1 or 2 • alkoxycarbonyl group of carbon number 1-4 • acetylamino group • carboxyl group or amino group, pyridylmethyl group optionally substituted by an alkyl group of carbon number 1-4, morpholyl methyl group, triazolylmethyl group, furylmethyl group, thienylmethyl group, pyrimidinylmethyl group, pyrazinylmethyl group, pyrrolylmethyl group, imidazolylmethyl group, quinolylmethyl group, indolylmethyl group, naphthylmethyl group, benzoyl group, α-hydroxybenzyl group, or an alkoxycarbonyl group of carbon number 1 or 2;

R^5 denotes a hydrogen atom or methyl group;

when R^1, R^2, R^3 and R^5 are simultaneously hydrogen atoms, R^4 is not hydrogen atom, benzyl group, 4-diethylaminobenzyl group or furylmethyl group).

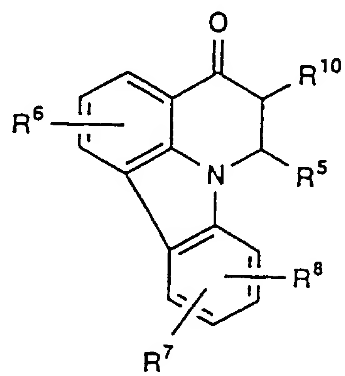
8. A preventive or therapeutic agent of a disease wherein a cyclic GMP- phosphodiesterase inhibiting action is effective, containing a compound represented by formula (I) or a salt thereof.

9. A drug containing a compound in accordance with any one of Claims 1-4 or a salt thereof as the effective component.

[An amendment for Claim 5 was received on the 24th of March 1999: The other claims were not altered]

Amended Claim 5

5. A compound or a salt thereof represented by following formula (IV), useful for the synthesis of the aforesaid compound of formula (I) or a salt thereof.



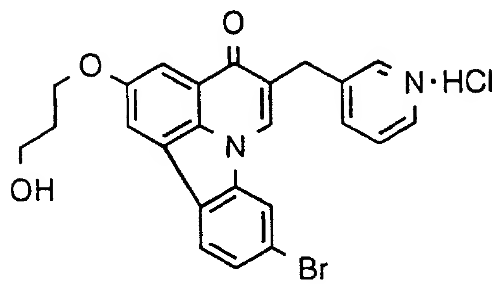
(IV)

(in the formula, R^5 is a hydrogen atom or methyl group, R^6 denotes a hydrogen atom, halogen atom, cyano group, optionally protected carboxyl group, optionally protected carboxymethyl group, alkoxycarbonyl group of carbon number 1-4, carbamoyl group, acetylamino group, 3-carboxy-1-propenyl group, optionally protected hydroxy group, optionally protected mercapto group, straight chain or branched chain alkyl group of carbon number 1-4 optionally substituted by one hydroxy group, an amino group optionally mono- or di-substituted by an alkyl group of carbon number 1-4, alkylthio group of carbon number 1-3, or straight chain alkoxy group of carbon number 1-6 optionally substituted by a 4-methoxyphenoxy group; R^7 denotes a hydrogen atom, optionally protected hydroxy group, optionally protected mercapto group, optionally protected amino group, cyano group, nitro group, trifluoromethyl group, trifluoromethoxy group, optionally protected carboxyl group, straight chain or branched chain alkanoyl group of carbon number 1-4, straight chain or branched chain alkyl group of carbon number 1-4, straight chain or branched chain alkoxy group of carbon number 1-4; R^8 denotes a hydrogen atom, halogen atom, optionally protected hydroxy group, or straight chain or branched chain alkoxy group of carbon number 1-4; R^{10} denotes a hydrogen atom, halogen atom, phenoxy group, an α-hydroxybenzyl group, anilino group, N-methylanilino group, methyl group, or halomethyl group; moreover, when R^5, R^6 and R^{10} are simultaneously hydrogen atoms and one of R^7 and R^8 is a hydrogen atom, then the other one is not a hydrogen atom or a chlorine atom).

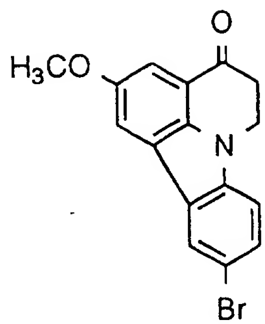
Simple Description of the Amendment Based on Treaty Clause 19

Claim 5 has been reduced in accordance with Clause 19 of the Patent Cooperation Treaty. This amendment removes specific compounds given in the International Search Report from Claim 5, and this will not exceed the range of disclosure in the International Application at the time of Filing.

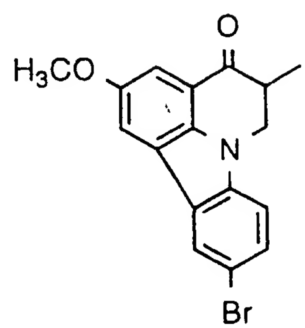
Figure 1



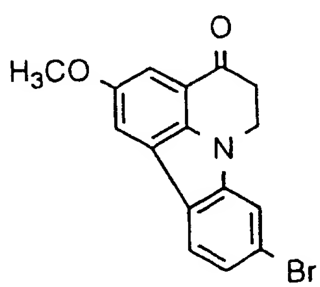
Example 278



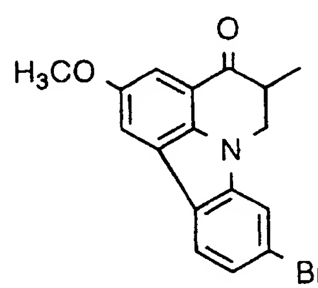
Example 1, Step 3



Example 48, Step 2

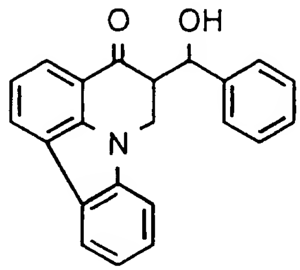


Example 101, Step 6

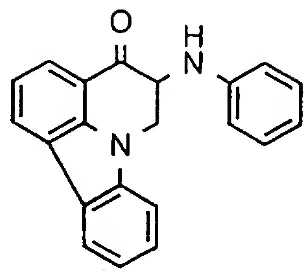


Example 113, Step 2

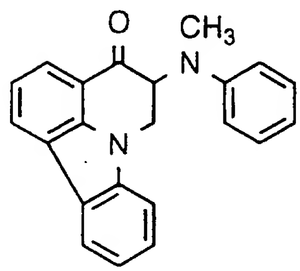
Figure 2



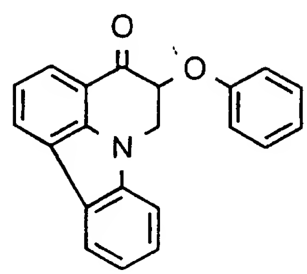
Example 145, Step 1



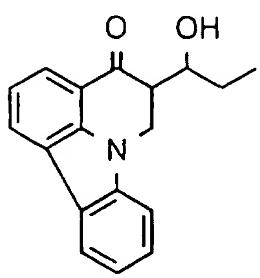
Example 147, Step 1



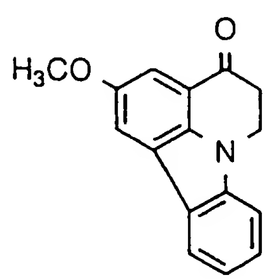
Example 148, Step 1



Example 149, Step 1

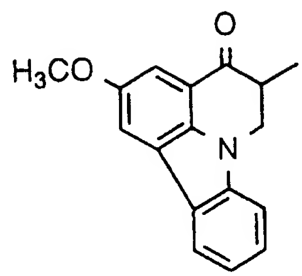


Example 151, Step 1

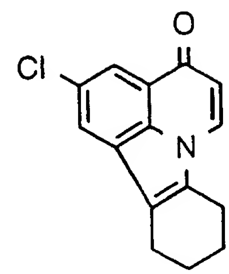


Example 154, Step 1

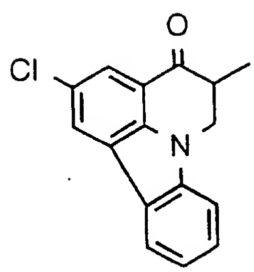
Figure 3



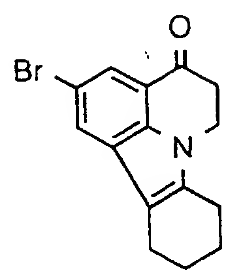
Example 161, Step 1



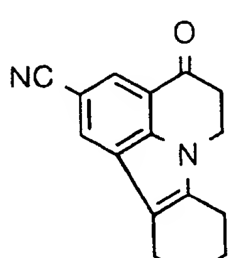
Example 171, Step 3



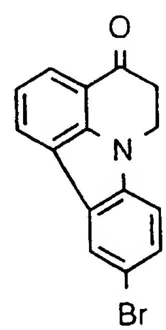
Example 172, Step 1



Example 173, Step 2

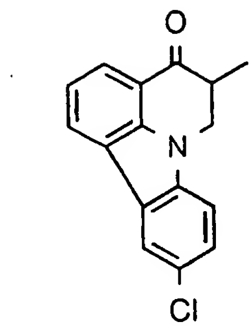


Example 173, Step 3

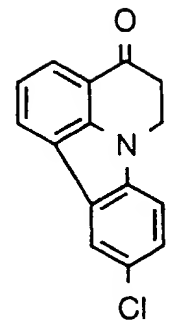


Example 184, Step 1

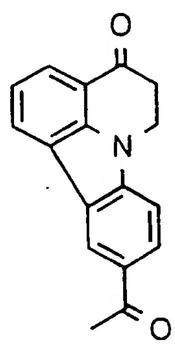
Figure 4



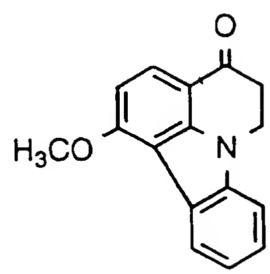
Example 190, Step 1



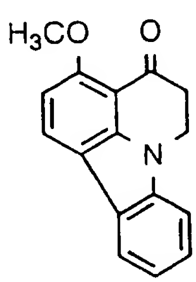
Example 193, Step 1



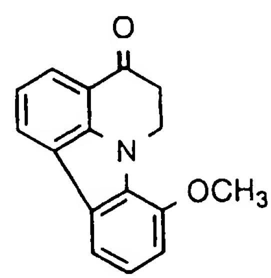
Example 194, Step 1



Example 203, Step 1

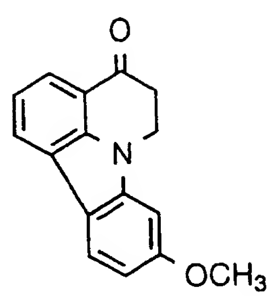


Example 210, Step 1

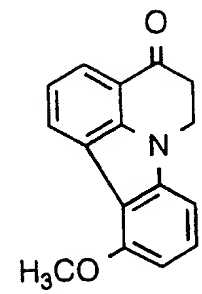


Example 216, Step 1

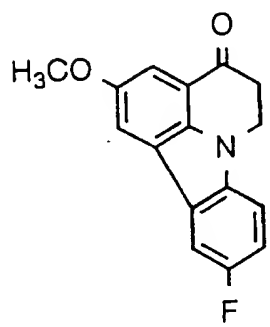
Figure 5



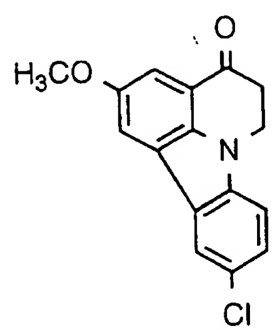
Example 224, Step 1



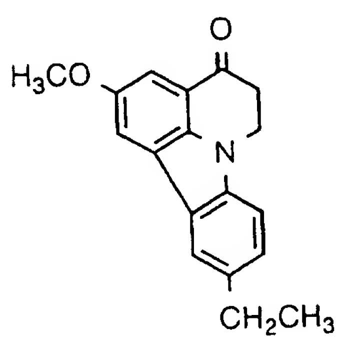
Example 232, Step 1



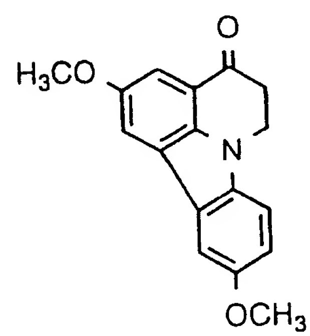
Example 235, Step 4



Example 243, Step 3

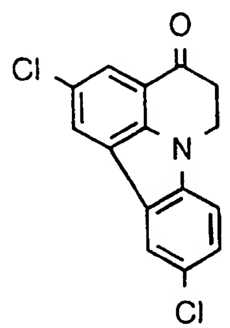


Example 248, Step 4

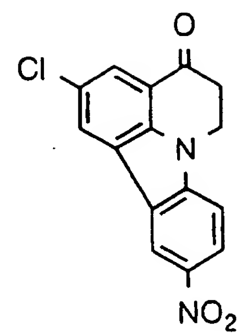


Example 257, Step 1

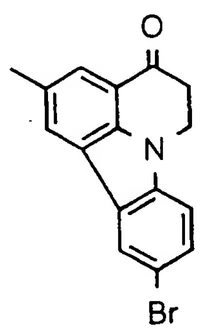
Figure 6



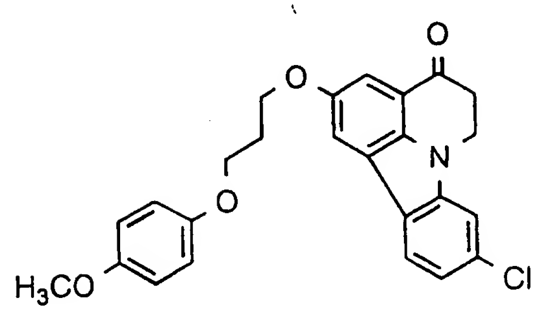
Example 265, Step 2



Example 272, Step 4



Example 276, Step 4



Example 283, Step 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/04307

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl[6] C07D471/04, A61K31/435, 31/44, 31/495, 31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl[6] C07D471/00-471/22, A61K31/435, 31/44, 31/495, 31/505

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA(STN), REGISTRY(STN), MEDLINE(STN), WPIDS(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO, 97/45427, A1 (Mochida Pharmaceutical Co., Ltd.), December 4, 1997 (04. 12. 97), Full text (Family: none)	1 - 9
X	Harter, H. et al., "Schmidt-reaction of tetrahydroquinolone derivatives.", Chimia, 1976, Vol. 30, No. 2, pages 50-52	5
X	El-Ahl, A. et al., "A facile and convenient synthesis of substituted tetrazole derivatives from ketones or α,ß-unsaturated ketones.", Tetrahedron Letters, 1995, Vol. 36, No. 40, pages 7337-7340	5
A	Henry R. et al., "4-Oxo-5,6-dihydro-4H-pirido(3,2,1-jk)carbazole and its Aralkylidene Derivatives.", J. Org. Chem., 1959, Vol. 24, pages 324-327	1 - 9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
February 12, 1998 (12. 02. 98)	February 24, 1998 (24. 02. 98)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.